"EVALUATION OF THE EFFICACY OF INTRANASAL SALMON CALCITONIN NASAL SPRAY AS A BONE MINERALIZING AGENT AFTER OPEN REDUCTION AND INTERNAL FIXATION IN PATIENTS WITH MANDIBULAR FRACTURES: A PROSPECTIVE CLINICAL STUDY"

Dissertation submitted to

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In partial fulfillment of the requirement for the degree of

MASTER OF DENTAL SURGERY

In the speciality of

ORAL AND MAXILLOFACIAL SURGERY

By

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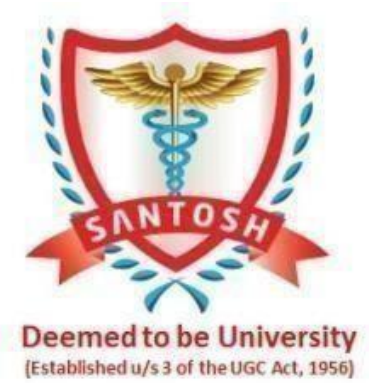

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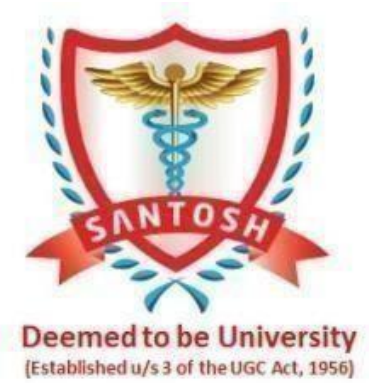

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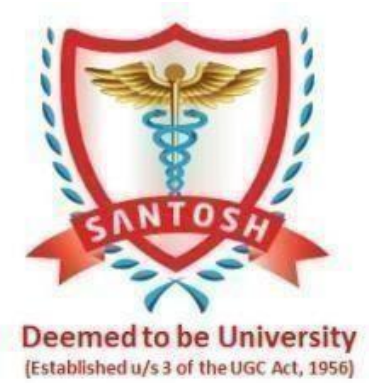

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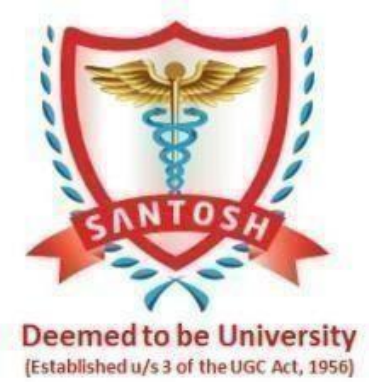

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ANTI -PLAGIARISM DECLARATION/UNDERTAKING

I, **Dr. Rani Raginee Rajhans** hereby declare that the present thesis entitled, **"THE EVALUATION OF THE EFFICACY OF INTRANASAL SALMON CALCITONIN NASAL SPRAY AS A BONE MINERALIZING AGENT AFTER OPEN REDUCTION AND INTERNAL FIXATION IN PATIENTS WITH MANDIBULAR FRACTURES: A PROSPECTIVE CLINICAL STUDY"** submitted by me to Santosh Deemed to be University is a bonafide/original research work. I also hereby declare that there is no plagiarism, and the present research work has not been submitted for the award of any degree/diploma of the same Institution where the work was carried out or to any other Institution.

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Dr. Rani Raginee Rajhans

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LIST OF ABBREVIATIONS

S.NO.	ABBREVIATIONS	FULL FORM
1	IMF	Intermaxillary Fixation
2	PRP	Platelet Rich Plasma
3	BMP	Bone Morphogenetic Protein
4	PDGF	Platelet-Derived Growth Factor
5	TGF-ß	Transforming Growth Factor ß
6	VEGF	Vascular Endothelial Growth Factor
7	MSC	Mesenchymal Stem Cells
8	HA	Hydroxyapatite
9	ß-TCP	ß-Tricalcium Phosphate
10	ORIF	Open Reduction and Internal Fixation
11	EMA	European Medicines Agency
12	FDA	Florida Dental Association
13	IU	International Unit
14	CTx	C-terminal telopeptide of Type I Collagen
15	BMD	Bone Mineral Density
16	NSAIDS	Non-Steroidal Anti-Inflammatory Drugs
17	VAS	Visual Analogue Score
18	ELISA	Enzyme-Linked Immunosorbent Assay
19	iPTH	intact Parathyroid Hormone
20	ENT	Ear, Nose & Throat
21	IBD	Inflammatory Bowel Disease
22	SASD	Supercritical Fluid Assisted Spray Drying
23	LSS	Lumbar Spinal Stenosis
24	OPG	Orthopantomogram
25	SCT	Salmon Calcitonin
26	CGCG	Central Giant Cell Granuloma
27	ZMC	Zygomaticomaxillary Complex
28	GA	General Anesthesia
29	LA	Local Anesthesia
30	IBM SPSS	Statistical Package for the Social Sciences
31	SD	Standard Deviation
32	DEXA	Dual Energy X-ray Absorptiometry
33	MTC	Medullary Thyroid Carcinoma
34	LCS	Lumbar Canal Stenosis

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INTRODUCTION

Reconstruction of maxillofacial trauma is an intriguing and complex feat for maxillofacial surgeons, requiring planned and meticulous surgeries, especially in the modern world when high velocity motor vehicle accidents and other traumas are on constant rise. Trauma to the maxillofacial complex is debilitating to the patient, functionally, aesthetically, and psychologically. A deformed face not only leads to difficulty in speech, swallowing, vision or smell, but also leads to social anxiety and depression. Rehabilitation of maxillofacial trauma is constantly evolving, focusing especially on restoration of function and form by incorporation of latest available resources. Mandibular fractures account for 57% of all maxillofacial trauma, especially in developing countries like India.[1] The mandible is the biggest bone in the viscerocranium. The mandible articulates with the surrounding bones through a synovial joint known as the temporomandibular joint. These movements result in complicated processes such as mastication and speaking.

Mandibular fractures are associated with varying degree of injury to muscles, due to stripping of the periosteum, which leads to the changes in its bony architecture.[2] Trauma to the muscles of mastication could invariably affect the masticatory efficiency and the normal range of motion of the individual. Fractured mandible and encompassing structures attenuate its load bearing capacity, which invariably reduces the functional capacity of the patient.[3] The ability of a patient to masticate reduces drastically even after a minor dentoalveolar surgery.[4]

The metabolic and endocrine needs are raised by a general systemic reaction to trauma or extreme surgical stress. This results in a significant alteration in the metabolism of proteins and energy due to the increased synthesis of hormones such glucagon, insulin, cortisol, catecholamines, vasopressin, and aldosterone. Without sufficient nutritional assistance, these patient's energy needs for recovery are mostly satisfied by the breakdown of body protein, which results in a loss of lean body mass.[5-7]

Hence, the return to function is important for improvement of masticatory efficiency since it contributes to the improvement of general physical health of the patient. The complications arising due to mandibular fractures include malocclusion, trismus, paresthesia, limited range of motion, internal joint derangement, chronic pain, malunion,

nonunion and joint ankylosis which makes it difficult for the patient to regain their entire function.[4] Both open and closed procedures are used to treat mandibular fractures. Closed procedures leave the mandible with an architectural aberration (malunion) and do not guarantee sufficient anatomic reduction of the fracture.[8] Open reduction includes repositioning of the mandibular fractured segments and stabilizing it in its pre-traumatic position. Open reduction and internal fixation proponents assert quicker occlusal function restoration, optimal realignment of fractured segments, and financial benefits from shorter recuperation times thereby allowing earlier return to work. Proponents of closed treatment assert that their treatments are less traumatic, retain the blood flow of the site, and allow for a shorter hospital stay.[9] There exists a bias for the preferential use of open reduction in cases of more complicated fractures among surgeons, since adequate restoration of anatomy is achieved under vision. In intermaxillary fixation (IMF) procedures, a surgeon relies mostly on ancillary parameters for restoration of anatomy, hence, there persists a reluctance to its use for more complicated fractures. [10]

Research has focused on natural and synthetic materials to stimulate bone formation, improve structural integrity, and reduce complications such as delayed union and non-union. Natural materials derived from biological sources include autologous bone grafts, PRP and BMPs. Autologous bone grafts, often harvested from the iliac crest, rib, or tibia, provide osteogenic cells, bone matrix proteins, and essential minerals.[11,12] While they offer high osteogenic potential and no risk of immune rejection, their limitations include limited availability, donor-site morbidity, and prolonged healing time at the harvest site. PRP, a blood-derived product rich in growth factors such as transforming growth factor-beta (TGF-β), platelet-derived growth factor (PDGF), & vascular endothelial growth factor (VEGF), enhances osteogenesis, stimulates angiogenesis, and reduces inflammation, particularly benefiting patients with osteoporosis or diabetes.[13] Similarly, BMPs, specifically BMP-2 and BMP-7, stimulate mesenchymal stem cells (MSCs) differentiate into osteoblasts, thereby inducing bone formation. BMPs are often combined with scaffolds or grafts in cases of large bone defects or critical-sized fractures.[14]

Synthetic materials such as calcium phosphate ceramics, including HA and β-TCP, mimic the mineral composition of bone and are widely used as bone graft substitutes.[15] These materials facilitate osteointegration and bone remodeling but have a brittle nature

and lower mechanical strength compared to natural bone. Salmon calcitonin has gained attention as a promising adjunctive therapy due to its dual effects on bone metabolism and pain management.[16] It enhances bone regeneration by inhibiting osteoclast activity, reducing bone resorption, and promoting osteoblast-mediated bone formation. By facilitating callus development, mineral deposition, and structural integrity, calcitonin helps prevent delayed union and non-union. Additionally, it has potent analgesic effects, modulating central pain pathways and promoting natural pain suppression through endorphin release, thereby reducing postoperative discomfort and improving mobility.

Beyond maxillofacial trauma, calcitonin is widely used in conditions such as osteoporosis, where it prevents bone loss in postmenopausal women and elderly patients, Paget's disease, where it regulates abnormal bone remodeling and alleviates bone pain, and hypercalcemia, especially in malignancies, where it lowers elevated blood calcium levels by increasing renal calcium excretion and inhibiting osteoclastic activity.[16] Calcitonin is available in multiple formulations, with intranasal delivery being the preferred route due to its high bioavailability, ease of administration, and non-invasive nature.[17] Compared to subcutaneous or intramuscular injections, which are effective but have lower patient compliance, the intranasal route eliminates the need for injections and improves treatment adherence.[18] Intravenous administration is reserved for acute cases of hypercalcemia, where rapid calcium-lowering effects are needed. The nasal spray formulation offers rapid absorption through the nasal mucosa, ensuring efficient systemic bioavailability while minimizing gastrointestinal side effects.[19] Despite its potential benefits in maxillofacial trauma, research on intranasal salmon calcitonin in oral and maxillofacial regions remains limited. Given its dual role in bone regeneration & pain relief, salmon calcitonin could significantly enhance surgical outcomes in patients with mandibular fractures.[18,19] It is particularly beneficial for the patient with osteoporosis, diabetes, or other systemic conditions affecting bone metabolism. Additionally, calcitonin may help reduce postoperative complications, including infection, malocclusion, and delayed healing, which are common challenges in maxillofacial trauma management. [19]

Bone healing is influenced by biological and mechanical factors, which can significantly impact the rate and quality of fracture recovery. Biological factors such as diabetes, osteoporosis, hypertension, and malnutrition can impair bone remodeling, while

hormonal imbalances, including thyroid dysfunction and estrogen deficiency, affect calcium metabolism and osteoblast function.[20] Additionally, smoking and alcohol consumption negatively impact vascularization and osteoblastic activity, further delaying healing. Mechanical factors such as fracture stability and load-bearing efficiency also play a critical role in bone regeneration, as proper alignment and fixation prevent excessive micro movements, which can impede callus formation. The mechanical environment of the fracture site directly influences bone remodeling, making stability a key component of successful healing. Despite advancements in surgical methods and fixation materials, complications such as delayed healing, infection, and reduced functional recovery persist, particularly in patients with systemic health conditions or poor bone metabolism.[4] As a result, there is an increasing need for adjunctive pharmacological treatments that can accelerate bone regeneration, minimize complications, and improve overall patient outcomes.

While traditional treatments such as closed reduction and ORIF provide mechanical stability, they do not directly enhance the biological conditions required for optimal osteogenesis. As a result, natural and synthetic materials have been extensively researched for their ability to stimulate bone formation, improve structural integrity, and minimize complications such as delayed union and non-union.[14] bone matrix proteins, and mineral components essential for bone formation. While they offer high osteogenic potential and no risk of immune rejection, their limitations include limited availability, donor-site morbidity, and prolonged healing time at the harvest site.[21] Similarly, BMPs, specifically BMP-2 and BMP-7, play a crucial role in stimulating mesenchymal stem cells (MSCs) to differentiate into osteoblasts, thereby inducing bone formation. BMPs are often used in combination with scaffolds or grafts in cases of large bone defects or critical-sized fractures [14]

Because of their accessibility, biocompatibility, and ability for integration with host bone. Synthetic materials which are designed to resemble genuine bone tissue offer osteoconductive scaffolding for the development of new bone and are frequently utilized in orthopedic and maxillofacial streams. Calcium phosphate ceramics, such HA and β-TCP, are frequently utilized as alternatives to bone grafts.[12] These materials facilitate osteointegration and bone remodeling but have a brittle nature and lower mechanical strength compared to natural bone. Salmon calcitonin has gained attention as a promising

adjunctive therapy in fracture healing and pain management due to its dual effects on bone metabolism and analgesia.[16] By suppressing osteoclast activity, it lowers bone resorption and stops excessive bone loss, which is a key factor in improving bone regeneration. By blocking osteoclastic breakdown, calcitonin indirectly promotes osteoblast-mediated bone formation, facilitating callus development and mineral deposition at the fracture site. Additionally, calcitonin enhances calcium deposition, which is essential for fracture consolidation and structural integrity.[17] Beyond its osteoprotective properties, salmon calcitonin exhibits potent analgesic effects that significantly contribute to post-operative recovery. It modulates central pain pathways, reducing hyperalgesia by acting on receptors in the central nervous system. Furthermore, calcitonin enhances endorphin release, which plays a role in natural pain suppression, reducing postoperative discomfort and improving patient mobility and functional recovery.

Besides maxillofacial trauma, calcitonin has been extensively used in other medical conditions due to its ability to regulate bone metabolism and calcium homeostasis. In osteoporosis, it serves as a therapeutic agent that prevents bone loss by inhibiting osteoclast-mediated resorption, making it particularly beneficial for postmenopausal women and elderly patients at risk for fractures. In Paget's disease, calcitonin regulates abnormal bone remodeling, helping to alleviate bone pain and excessive bone turnover. Additionally, in cases of hypercalcemia, especially those associated with malignancies, calcitonin helps reduce elevated blood calcium levels by increasing renal calcium excretion and inhibiting osteoclastic bone resorption, thereby restoring calcium balance.[21]

Calcitonin can be administered via various routes, with intranasal delivery being the preferred method due to its high bioavailability, ease of administration, and non-invasive nature.[16] Compared to subcutaneous or intramuscular injections, which are effective but have lower patient compliance due to pain and inconvenience, the intranasal route eliminates the need for injections and provides a more patient-friendly alternative.[17] Intravenous administration is primarily reserved for acute cases of hypercalcemia, where rapid calcium-lowering effects are required. Nasal spray formulation offers several advantages, including rapid absorption through the nasal mucosa, ensuring efficient systemic bioavailability. Unlike oral medications, which may cause gastrointestinal side

effects, intranasal calcitonin minimizes digestive discomfort while enhancing treatment adherence among patients, making it a preferred option for long-term use.[17]

The rationale for investigating intranasal salmon calcitonin as an adjunct to ORIF is as a result of paucity in research on use of salmon calcitonin nasal spray in oral and maxillofacial regions. Salmon calcitonin based on its dual role in bone regeneration and pain relief. [21] By enhancing bone healing in patients sustaining mandibular fractures and reducing postoperative pain, calcitonin has the potential to significantly improve surgical outcomes, particularly in patients with compromised bone metabolism such as those with osteoporosis, diabetes, or other systemic conditions.[17,18] In postoperative complications, including infection, malocclusion and delayed healing; which are common challenges in maxillofacial trauma management.

AIM AND OBJECTIVES

AIM:

- This study aims to evaluate the efficacy of salmon calcitonin nasal spray on bone healing following open reduction and internal fixation in patients with mandibular fractures.

OBJECTIVES:

- To radiographically evaluate the healing efficiency of the fracture site in patients with mandibular fracture.
- To compare the difference between biochemical levels of plasma osteocalcin preoperatively and postoperatively.
- To evaluate and compare post-operative pain between the groups.
- To observe any complications associated with the administration of calcitonin nasal spray.

HISTORY

- Calcitonin nasal spray has long been used to treat osteoporosis and other bone-related diseases.[13]
- 1960s Discovery of Calcitonin: It is a hormone involved in calcium and bone metabolism, was discovered in 1962. Originally produced from salmon, it has a stronger and longer-lasting action than human calcitonin.[20]
- 1970s–1980s: Synthetic and recombinant salmon calcitonin have been produced and approved as an injectable treatment for osteoporosis, Paget's disease, and hypercalcemia.[20]
- In response to patient discomfort with injections, researchers created Miacalcin (Novartis), the first FDA-approved calcitonin nasal spray for postmenopausal osteoporosis in 1995. According to studies, nasal sprays are equally effective as injections and have better patient adherence.[17]
- In the 2000s, research raised concerns about calcitonin's limited fracture prevention benefits compared to newer osteoporosis drugs like bisphosphonates. Some studies indicated a potential link to an increased cancer risk.[13]
- In 2012-2013, the European Medicines Agency (EMA) and FDA implemented regulatory restrictions and later reviewed safety data, concluding that the risks outweighed the benefits. The EMA recommended limiting calcitonin use to short-term treatment. In 2013, the FDA also advised against long-term use due to cancer concerns.[14]
- A meta-analysis by Wells et al. (2015) found no significant link between calcitonin use and cancer, confirming its safety for long-term use with minimal oncogenic risk.[15]

REVIEW OF LITERATURE

Gagel R, Logan C, Mallette LE (1988)[22] conducted a prospective, randomized controlled trial to compare a new freshly prepared intranasal preparation of salmon calcitonin to subcutaneous drug in 18 patients with Paget's disease using two different protocols. In the first protocol, 15 patients who were not previously administered with salmon calcitonin were given the agent for 3 months by either the intranasal or subcutaneous route. Seven patients treated with intranasal calcitonin had a mean fall in the serum alkaline phosphatase of 33% over 3 months compared to a fall of 40% in the subcutaneously treated group; the difference between the two treatment groups was not statistically significant. In the second protocol, three patients previously stabilized on subcutaneous calcitonin were switched to nasal spray with no subsequent change in alkaline phosphatase values during 6 months of treatment. These results demonstrate that intranasal salmon calcitonin is effective in lowering the serum alkaline phosphatase in Paget's disease. Ease of administration and patient acceptance make intranasal calcitonin a reasonable alternative for geriatric patients. They reported that the largest declines in Serum alkaline phosphatase were found in a patient taking only 100 IU salmon calcitonin nasal spray, but the pain decreased in both groups. Subcutaneous administrations were associated with few side effects such as flushing of face and hands, itching of palms, nausea and dizziness, whereas those under the intranasal administration experienced transient tingling or stinging sensation followed by sneeze, rhinorrhea and nasal ulceration. Hence, they found that the intranasal route was effective because with oral administration, calcitonin becomes degraded by gastric acids due to its polypeptide structure. Calcitonin nasal spray overcomes all these limitations because it was absorbed directly through the nasal mucosa into the bloodstream, bypassing the first pass metabolism in the liver. Therefore, the peak plasma level of the drug was attained within an hour of spray administration. Thus, intranasal calcitonin ensures better bioavailability as well as efficient in lowering Serum alkaline phosphatase along with better compliance in geriatric patients due to ease of administration.

Darakchiev BJ, Bulas RV, Dunsker SB (2000)[23] investigated the efficacy of nasal calcitonin therapy in facilitating bone union and clinical recovery in an 85-year-old female patient with an odontoid fracture and multiple comorbidities. The patient, at high surgical

risk, received calcitonin therapy as an alternative approach. The authors reported that low serum calcium levels led to decreased endogenous calcitonin, suggesting that exogenous calcitonin administration could maintain physiological balance and potentially enhance bone turnover in osteoporotic patients. They recommended a dosage of 100-200 IU/day for osteoporosis, with maximal skeletal response observed during the initial 18-24 months of therapy. Evaluation at eight weeks demonstrated significant analgesic effects and improved bone healing outcomes.

Chesnut CH, Silverman S, Andriano K et al. (2000)[24] conducted a five-year, double-blind, randomized controlled trial involving 1255 postmenopausal osteoporotic women to assess the efficacy of salmon calcitonin nasal spray in reducing vertebral fractures. Participants were administered nasal calcitonin at doses of 100, 200 and 400 IU, compared to a placebo group receiving calcium (1000 mg) and vitamin D (400 IU). The group receiving 200 IU calcitonin showed a notable 33% reduction in vertebral fracture risk and a 12-14% inhibition of bone turnover compared to the placebo group. These findings support the use of 200 IU calcitonin nasal spray as an effective intervention for fracture risk reduction in postmenopausal osteoporotic women.

Huusko TM, Karppi P, Kautiainen H et al. (2002)[25] examined the role of calcitonin in pain management, fracture fusion, and functional outcomes in patients with hip fractures in a randomized controlled trial. The study demonstrated a significantly higher fracture union rate in the calcitonin group (84%) compared to the placebo group (63%) at three months post-treatment ($p=0.029$). The findings underscore calcitonin's potential to accelerate bone healing and provide analgesic benefits, especially in geriatric patients undergoing internal fixation. However, further clinical trials are necessary to establish its definitive role in fracture care protocols.

Srivastava AK, Libanati C, Hohmann O et al. (2004)[26] explored the acute effects of nasal calcitonin on bone resorption in elderly women with osteopenia. Their findings revealed a significant reduction in C-telopeptide of type I collagen (CTx) levels by 33% within 60 days of treatment, emphasizing calcitonin's rapid antiresorptive action. The study suggests that calcitonin is a viable option for preventing bone loss in older adults with osteopenia, particularly given its favorable safety profile and ease of administration.

Toth E, Csupor E, Meszaros S et al. (2004)[27] conducted an open-label trial to assess the impact of calcitonin nasal spray on bone mineral density (BMD) in 71 male patients with idiopathic osteoporosis. After treatment, notable increases in BMD at the lumbar spine and femoral neck were observed, filling a critical gap in the management of male osteoporosis. Calcitonin therapy was particularly beneficial for patients unable to tolerate or access bisphosphonates, demonstrating a substantial impact on BMD enhancement and fracture risk reduction.

Podichetty VK, Segal AM, Lieber M et al. (2004)[28] conducted a double-blind, randomized controlled trial to evaluate the analgesic efficacy of salmon calcitonin nasal spray in patients with lumbar canal stenosis. Contrary to its proven benefits in osteoporosis, calcitonin did not demonstrate significant improvements in pain relief, walking distance, or functional outcomes in spinal stenosis patients compared to placebo. These findings highlight the necessity for condition-specific treatment protocols, suggesting that calcitonin's therapeutic benefits are more pronounced in bone-related pathologies rather than neurogenic conditions.

Peichl P, Marteau R, Griesmacher A et al. (2004)[29] performed a 12-month clinical trial to investigate the effect of calcitonin nasal spray in postmenopausal women with hip fractures managed with cementless total hip arthroplasty. The study revealed that twice-daily administration of 200 IU calcitonin, combined with calcium and vitamin D, significantly improved BMD, reduced pain scores on the VAS scale and lowered the incidence of periprosthetic ossifications. These findings suggest that calcitonin is a valuable adjunct therapy in fracture management, particularly as an alternative to hormone replacement therapy and bisphosphonates.

El-Husseini AA, Agroudy AE, Sayed MF et al. (2004)[30] conducted a prospective study to investigate the combined effect of alendronate, alfacalcidol, and salmon calcitonin nasal spray on bone mineral density (BMD) in young renal transplant recipients diagnosed with osteopenia and osteoporosis. The study enrolled patients who were receiving immunosuppressive therapy, a known risk factor for bone loss. Over a 12-month follow-up period, lumbar spine T-scores significantly improved from -2.3 to -1.0 in those receiving the combination therapy. The regimen was well-tolerated with minimal adverse effects, indicating a favourable safety profile. The authors highlighted the therapeutic potential of

calcitonin as an adjunct in managing transplant-related bone loss, particularly in individuals who are at increased risk of fracture due to corticosteroid use. However, the study presents certain limitations, including a relatively small sample size and the absence of a control group receiving calcitonin monotherapy, which limits the ability to isolate the specific impact of calcitonin. Additionally, the duration of the study may not have been sufficient to assess long-term outcomes or potential adverse effects associated with prolonged calcitonin use. Despite these limitations, the study provides valuable insights into the potential role of calcitonin as part of a combination therapy for mitigating osteoporosis in renal transplant patients, warranting further investigation in larger, randomized controlled trials.

Kaskani E, Lyritis GP, Kosmidis C et al. (2005)[31] conducted a 1-year, prospective, randomized controlled pilot study to evaluate the effects of intermittent administration of 200 IU intranasal salmon calcitonin combined with low doses of 1α(OH) vitamin D3 on bone mineral density (BMD) and biochemical markers of bone turnover in postmenopausal women with osteoporosis. A total of 102 women were randomized to receive either the calcitonin regimen or vitamin D3 and calcium alone. The calcitonin group received treatment for one month followed by one month off throughout the study period. Results showed significant improvements in BMD at the lumbar spine (3.0%, p=0.005) and femoral neck (3.1%, p=0.0005) in the calcitonin-treated group compared to baseline and the control group. Biochemical markers, including urinary calcium/creatinine and Pyrilinks-D/creatinine ratios, decreased significantly in the calcitonin group, indicating a reduction in bone turnover. Additionally, a notable decrease in serum iPTH levels (2.5%, p=0.005) was observed in the calcitonin group. The study underscores the potential benefits of intermittent calcitonin administration in preventing bone loss in postmenopausal osteoporosis while minimizing potential side effects associated with continuous administration, such as receptor downregulation and the "escape phenomenon." However, the study is limited by its small sample size and lack of long-term follow-up to assess fracture risk reduction and sustained efficacy. Further studies with larger cohorts and extended follow-up are recommended to validate these findings.

Tafazal SI, Ng L, Sell P (2006)[32] conducted a double-blind, randomized controlled trial to evaluate the efficacy of salmon calcitonin nasal spray for managing lumbar spinal stenosis in a cohort of 40 patients. The study aimed to assess the analgesic effects and

impact on functional outcomes of calcitonin compared to a placebo. Despite the established benefits of calcitonin in osteoporosis-related pain management, the findings revealed no significant improvement in pain relief, walking distance, or functional scores in the calcitonin group compared to the placebo group. These results align with other studies indicating that calcitonin may have limited efficacy in managing non-skeletal pain conditions such as spinal stenosis. The study's limitations include a relatively small sample size and short follow-up duration, which may have affected the ability to detect potential longer-term benefits. Additionally, the study did not assess the impact of calcitonin on bone mineral density or fracture risk, aspects that are typically relevant in calcitonin therapy. Despite these limitations, the study underscores the importance of condition-specific treatment protocols, suggesting that the therapeutic benefits of calcitonin may be more pronounced in bone-related pathologies rather than neurogenic conditions like lumbar spinal stenosis.

Chatziavramidis A, Mantsopoulos K, Gennadiou D et al. (2008)[33] presented a review of nasal complications associated with the use of intranasal calcitonin (InC) in postmenopausal women with osteoporosis, supplemented by two case reports. The study highlighted two cases of nasal septum perforation and septum-concha synechiae in women undergoing prolonged InC therapy. Both patients reported persistent nasal symptoms, including obstruction, crust formation, and occasional bleeding, which were attributed to long-term InC administration. The authors reviewed the literature on nasal complications of InC and identified various contributing factors, including local mucosal irritation, preservatives such as benzalkonium chloride, and antibody formation against calcitonin. The study underscored the importance of ENT evaluation before and during InC therapy to identify potential complications early and suggested that modifying the route of administration or switching to oral therapy may be necessary in patients with severe nasal symptoms. Despite the small sample size and observational nature of the study, the findings emphasize the need for ongoing monitoring of nasal health in patients receiving InC therapy, particularly those on long-term regimens. The authors concluded that while intranasal calcitonin remains an effective treatment for osteoporosis, its nasal side effects warrant further investigation to optimize safety and patient compliance.

Lee SL, Yu LX, Cai B et al. **(2010)**[34] studied and concluded that regulatory issues that generic synthetic salmon calcitonin nasal sprays face were covered in this study. The study

highlighted that contaminants and inconsistent peptide drug development make it challenging to achieve comparable safety and efficacy to brand- name formulations. The results highlight the need for strict regulatory requirements to approve generic medications based on peptides. Maintaining therapeutic efficacy and patient confidence in generic calcitonin requires consistent pharmacokinetics and bioavailability.

Sarrafan N, Mehdinasab SA, Dashtbozorg A et al. (2010)[35] examined the effect of salmon calcitonin nasal spray on fracture healing in older females with intertrochanteric femur fractures. According to their findings, by week three, 72% of patients in the calcitonin group had developed bone callus, while just 40% of patients in the placebo group had done so. These results demonstrated how calcitonin may be used as an adjuvant treatment to improve bone healing and encourage early fracture union in senior citizens. In postoperative therapy for fractures, calcitonin is a useful tool because it can speed up the healing process, especially in populations that are susceptible to delayed healing.

Mathias NR, Hussain MA (2010)[36] reviewed the potential of non-invasive systemic drug delivery routes, particularly focusing on intranasal, buccal/lingual pulmonary, and transdermal administration. The authors emphasized the importance of considering alternate routes of administration for drugs with poor oral bioavailability, extensive first-pass metabolism, or local gastrointestinal toxicity. Intranasal calcitonin was highlighted as a successful example of a peptide-based drug that bypasses hepatic metabolism and achieves therapeutic blood levels effectively. The review outlined several advantages of intranasal administration, such as rapid systemic absorption, avoidance of gastrointestinal degradation, and improved patient compliance. Additionally, it was noted that intranasal formulations of peptides like calcitonin offer a viable alternative to injections, particularly for chronic conditions such as osteoporosis. However, potential drawbacks include limited dose capacity, mucosal irritation, and inconsistent drug absorption. The authors recommended further research to optimize intranasal formulations by enhancing bioavailability and minimizing adverse effects. They also suggested that patient education on proper administration techniques is crucial to mitigate complications associated with nasal delivery. The review concluded that while intranasal drug delivery has proven effective for certain peptide drugs like calcitonin, more studies are needed to establish long-term efficacy and safety, particularly in comparison to other non-invasive routes such as

buccal and transdermal systems.

Karsdal MA, Henriksen K, Arnold M (2010)[37] conducted a randomized, placebo-controlled, double-blind trial to evaluate the efficacy and safety of intranasal calcitonin in improving bone mineral density (BMD) in children and adolescents with inflammatory bowel disease (IBD). The study enrolled 63 participants aged 8 to 21 years with spinal BMD Z-scores ≤ -1.0 SD, randomly assigned to receive either 200 IU of intranasal calcitonin or a placebo daily for 18 months. All participants also received calcium and vitamin D supplementation. Results indicated that while intranasal calcitonin was well-tolerated with minimal adverse effects, it did not significantly improve BMD Z-scores compared to the placebo group. Notably, a subgroup analysis of participants with Crohn's disease demonstrated a slight improvement in spinal BMD Z-score after 9 months of calcitonin treatment ($p = 0.02$); however, this effect was not sustained through the 18-month follow-up. The authors also assessed the impact of nutritional and clinical factors on bone mineral accrual. Factors such as higher baseline body mass index, lower baseline BMD, improved linear growth, and higher levels of serum albumin and haematocrit were associated with higher bone mineral accrual. Conversely, disease severity, immunomodulator use, and elevated inflammatory markers were associated with lower bone mineral accrual. Despite its tolerability, the study concluded that intranasal calcitonin did not provide a long-term benefit in improving BMD in children and adolescents with IBD. The authors recommended that future research focus on addressing modifiable factors such as nutrition, physical activity, and disease control to optimize bone health in this population.

Pappa HM, Saslowsky TM, Filip DR et al. (2011)[38] conducted a randomized, placebo-controlled, double-blind trial to evaluate the efficacy and safety of intranasal calcitonin in improving bone mineral density (BMD) in children and adolescents with inflammatory bowel disease (IBD). The study enrolled 63 participants aged 8 to 21 years with spinal BMD Z-scores ≤ -1.0 SD, randomly assigned to receive either 200 IU of intranasal calcitonin or a placebo daily for 18 months. All participants also received calcium and vitamin D supplementation. Studies indicated that while intranasal calcitonin was well-tolerated with minimal adverse effects, it did not significantly improve BMD Z-scores compared to the placebo group. Notably, a subgroup analysis of participants with Crohn's

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Chen T, Lai RF, Zhou ZY et al. (2012)[39] investigated the feasibility of using ultrasonography as a non-invasive method to monitor fracture healing in a rabbit model of mandibular fractures. The study aimed to compare the effectiveness of ultrasound imaging with conventional X-ray examination in assessing callus formation and fracture healing over 12 weeks. Thirty rabbit models with mandibular fractures were created, and the healing process was monitored at 1, 2, 4, 6, 8, and 12 weeks postoperatively using both X-ray and ultrasound imaging. Results indicated a strong correlation between ultrasound and X-ray findings, with a Spearman rank correlation coefficient of 0.892 ($p < 0.001$). Ultrasonography effectively detected callus formation earlier than X-ray imaging and provided superior visualization of soft tissue structures and vascularization at the fracture site. By the 8th and 12th weeks, ultrasound images demonstrated complete callus bridging and cortical bone continuity, findings that were consistent with X-ray results. The potential of ultrasound as a safe, non-invasive alternative to X-ray imaging for assessing fracture healing, particularly in paediatric and pregnant populations, where radiation exposure is a concern. The authors recommended further research to standardize ultrasound scoring criteria and explore its applicability in clinical settings for monitoring maxillofacial fractures, especially in cases where calcitonin nasal spray is used as an adjunctive treatment to enhance bone healing.

Wells G, Chernoff J, Gilligan JP (2015)[15] conducted a systematic review and meta-

analysis to assess the potential association between salmon calcitonin and cancer development. This study was prompted by concerns raised by regulatory agencies regarding a possible oncogenic effect of calcitonin, particularly following reports of increased prostate cancer incidence in patients receiving an investigational oral formulation of calcitonin. The meta-analysis incorporated data from multiple randomized controlled trials and observational studies, evaluating cancer risk in patients receiving salmon calcitonin via nasal spray, subcutaneous injection, and oral formulations. The findings indicated a weak but statistically significant association between calcitonin use and overall cancer incidence, with an odds ratio of 1.61 (95% CI, 1.11–2.34). Notably, the most reported malignancy was basal cell carcinoma, followed by prostate cancer. However, the authors emphasized the lack of a clear dose-response relationship, and the heterogeneity of cancer types observed. The review also discussed potential mechanisms of calcitonin-associated carcinogenesis, particularly its effects on cAMP-mediated signaling pathways and the activation of G-protein-coupled receptors. Despite these theoretical mechanisms, the authors concluded that the biological plausibility of calcitonin as a carcinogen remains questionable. Additionally, animal studies and post-marketing surveillance data did not provide robust evidence to support a causal link between calcitonin and cancer. The authors recommended that clinicians exercise caution in prescribing calcitonin, especially in patients with a history of malignancy or those requiring long-term treatment. Further research was advised to clarify the oncogenic potential of calcitonin and to determine its risk-benefit profile in osteoporosis and other bone-related conditions. Despite the regulatory concerns, the review underscored the continued clinical utility of calcitonin in specific patient populations, particularly for short-term pain relief in osteoporotic fractures.

Hegde V, Jo JE, Andreopoulou P et al. (2015)[40] conducted a comprehensive review of the impact of antiresorptive therapies, including calcitonin, on fracture healing in osteoporotic patients. The review aimed to elucidate the dual effects of calcitonin nasal spray as both an antiresorptive agent and a potential promoter of fracture healing. Calcitonin, a peptide hormone known for its inhibitory effects on osteoclasts, was highlighted for its ability to maintain bone density while potentially enhancing cartilage formation and biomechanical integrity in fracture sites. The authors emphasized that while bisphosphonates and denosumab may delay fracture healing due to their potent inhibition of bone turnover, calcitonin exerts a milder antiresorptive effect, allowing for ongoing bone

remodeling and callus formation. Additionally, calcitonin demonstrated analgesic effects, reducing pain in patients with vertebral fractures, which could facilitate earlier mobilization and rehabilitation. However, the review also noted inconsistencies in the literature regarding the efficacy of calcitonin in promoting fracture healing, particularly in non-osteoporotic fractures. The authors recommended further randomized controlled trials to establish optimal dosing regimens, treatment duration, and long-term outcomes of calcitonin nasal spray in fracture management, especially in osteoporotic patients undergoing maxillofacial surgery. They concluded that calcitonin nasal spray remains a valuable therapeutic option for managing fracture-related pain and enhancing bone healing in select patient populations, though its clinical utility may be limited compared to more potent antiresorptive agents.

Cho W, Kim MS, Jung MS et al. (2015)[41] investigated the creation of new intranasal powder formulations of salmon calcitonin utilizing spray-drying and supercritical fluid-assisted spray-drying (SASD) techniques. SASD-processed calcitonin has a greater bioavailability than standard spray-dried formulations. Smaller particle size and greater stability in the SASD formulation resulted in improved nasal absorption in rat models. SASD technology could improve calcitonin nasal delivery, potentially replacing present formulations, according to the study's findings.

Haddadi K, Asadian L, Isazade A (2016)[42] compared oral gabapentin and nasal calcitonin. Because of its quick onset of action and direct effects on bone pain, nasal calcitonin showed greater pain alleviation. For patients who are intolerant to systemic drugs like gabapentin, nasal calcitonin offers a viable substitute for treating LSS symptoms. Better pharmacokinetics are ensured by its intranasal distribution, which prevents first-pass metabolism and improves therapeutic results.

Tabrizi R, Fardisi S, Zamiri B et al. (2016)[43] conducted a double-blind clinical trial to assess the use of salmon calcitonin in decreasing the recurrence of central giant cell granuloma following curettage. The study was conducted on 24 patients, following the same age group, sex, location and tumor size in both groups. The study group population included seven patients having central giant cell granuloma in the maxilla and another four of who had central giant cell granuloma in the mandible were administered with 200 IU

once per day salmon calcitonin nasal spray along with curettage after surgery. Those in the control group included the population with seven having central giant cell granuloma in the maxilla, six had central giant cell granuloma in the mandible and were given a placebo once a day for three months along with curettage. However, there was an incidence of recurrences in eight patients, which comprised 1 from the study group to 7 from the control group. The authors concluded that 3 months of calcitonin nasal spray administration was effective in bone formation, also seen to reduce the recurrence frequency of central giant cell granuloma in both the maxilla as well as mandible.

Yazdani J, Khiavi RK, Ghavimi MA et al. (2019)[44] assessed intranasal calcitonin's ability to lessen postoperative pain after operating on maxillofacial fracture in this study. By day seven, calcitonin-treated patients had less reliance on acetaminophen, but their perceptions of pain intensity stayed mostly the same. The study emphasizes how calcitonin may lessen the need for postoperative analgesics, especially in trauma situations. To confirm its function in pain management following maxillofacial procedures, more research is necessary due to the small sample size.

Srinivasan A, Wong F, Karponis D. (2020)[45] discussed calcitonin's historical role in osteoporosis treatment, its declining use, and prospects. Calcitonin lowers vertebral fractures, but it has been mostly supplanted by bisphosphonates and monoclonal antibodies (denosumab). The intranasal formulation is chosen over injections due to higher patient compliance. Oral calcitonin formulations have a low bioavailability and have not shown greater efficacy in clinical trials. New research indicates that calcitonin may alleviate osteoporosis-related discomfort.

Roy A, Thulasiraman S, Panneerselvam E et al. (2021)[46] performed a randomized controlled trial to evaluate the efficacy of salmon calcitonin nasal spray on bone healing following open reduction and internal fixation. 14 patients were randomly divided into study and control groups following a standardized surgical protocol. The study group received salmon calcitonin nasal spray, one puff/day in alternate nostrils with 500 mg calcium and Vitamin D 500 IU for 30 days, whereas those in the control group were not given salmon calcitonin nasal spray. The evaluation was done based on postoperative pain on the VAS Scale, radiological assessment on OPG and biochemical assessment of serum

osteocalcin. Authors concluded that salmon calcitonin nasal spray proved to be an effective modality in the healing of the fractures as well as an excellent analgesic.

Li N, Gong YC, Chen J (2021)[47] researched on 12 randomized controlled studies (n=1068 participants) to determine the efficacy and safety of intranasal salmon calcitonin (sCT) for osteoporosis, thereby performing meta-analysis. sCT effectively decreased blood calcium while increasing serum creatinine and alkaline phosphatase levels. There is no substantial effect on lumbar and hip BMD. The combination of sCT with conventional medications (such as calcium and vitamin D) was not more beneficial than normal treatment alone. The study found that sCT has some biochemical benefits, but its influence on BMD is unknown, making it less effective than bisphosphonates.

Camarini C, Tolentino EDS (2022)[48] evaluated the efficacy of non-surgical treatments for central giant cell granuloma (CGCG), a benign but potentially aggressive jaw lesion. Analyzing 15 studies encompassing 145 patients, they found that therapies such as calcitonin, intralesional corticosteroids, and denosumab yielded positive outcomes. Specifically, calcitonin achieved complete remission in 30 out of 61 cases, while intralesional triamcinolone led to lesion size reduction in 39 of 68 cases. Denosumab, administered to four patients, resulted in inactive bone metabolism and ossification in three instances. However, 40% of patients required additional surgical intervention, highlighting the limitations of non-surgical approaches. Despite some side effects, particularly with interferon, the review suggests that non-surgical treatments can be effective alternatives or adjuncts to surgery, especially for patients where surgery is contraindicated or poses significant risks. The authors emphasize the need for individualized treatment plans and further research to optimize non-surgical protocols for CGCG management.

Abdul-Ghani S, Lathan EC, Miao A et al. (2023)[49] explored the therapeutic roles of calcitonin and strontium ranelate in osteoporosis, particularly in postmenopausal women. Calcitonin, a peptide hormone that inhibits osteoclastic bone resorption, has shown modest efficacy in increasing bone mineral density (BMD) in the lumbar spine and reducing vertebral fracture risk, with limited impact on non-vertebral fractures. It is primarily used for short-term management of acute pain following osteoporotic vertebral fractures, administered nasally, but its clinical utility is constrained by mild adverse effects and the availability of more effective alternatives. However, use of strontium ranelate is limited by

serious safety concerns, including cardiovascular and thromboembolic events, which led to regulatory restrictions and its market withdrawal in several countries, though it remains available in regions such as India. Overall, both agents are considered second-line treatments; calcitonin is preferred for short-term analgesic use, whereas strontium ranelate may be an option for patients intolerant to first-line therapies, requiring careful patient selection due to its risk profile.

Alparslan AL, Yildiz TG, Kozaci LD et al. (2023)[50] researched on thermoreversible sol-gel formulations for the intranasal delivery of salmon calcitonin (sCT), aiming to enhance its bioavailability compared to a commercial intranasal spray. Utilizing PEG 1500 and poloxamer 407 at various pH levels (3, 4, and 5), the researchers optimized formulations to gel at approximately 34°C, the temperature of nasal mucosa, ensuring effective mucoadhesion and sustained drug release. Among the tested formulations, 3A, 4A, and 5A showed appropriate gelation temperatures, with formulations at pH 3 and 4 maintaining better sCT stability. In vitro release studies indicated higher cumulative sCT release for formulations 3A and 4A, while in vivo testing in rabbits demonstrated that formulation 4A achieved a bioavailability ($AUC_{0 \rightarrow t_{last}}$: 0.743) close to that of the commercial product (0.856), with favorable pharmacokinetics and prolonged mucosal retention. Conversely, formulation 3A exhibited lower systemic absorption. The study highlighted the potential of formulation 4A as an effective intranasal delivery system for sCT and underscores the importance of pH in optimizing drug stability and release.

MATERIALS AND METHOD

SOURCE OF DATA:

The patients who reported to the Out-patient and In-patient department of Santosh Dental College & Hospitals, Ghaziabad and allied private hospitals with ZMC fracture were selected based on the following inclusion and exclusion criteria.

STUDY DESIGN:

Prospective clinical study.

ETHICAL CONSIDERATION

Ethical approval was obtained for the study from the Institutional Ethical Committee Santosh Deemed to be University. The study was conducted as per standard objective procedures for ethical standards on human subjects as per university guidelines. The patients were informed about the sequence of the procedure in detail, and informed consent was obtained from each patient in both the local language (Hindi) and English, explaining the nature of the surgical procedure and the study. A detailed case history, necessary radiographic and blood investigations before the surgery. After ruling out head and cervical spine injury, cases were planned for open reduction and internal fixation under general anesthesia. Patients were prepared for ORIF under GA. Fixation of the reduced fracture was performed. Patients were assured of their right to withdraw from the study at any time without any repercussions.

SAMPLE SIZE:

Based on the study design and statistician's inputs, the total enumeration of 18 cases was done based on the sample size of 9 in both control and study group where Group A: Consisted of patients who suffered mandibular fracture and were administered Salmon Calcitonin nasal spray for a period of 1 month. However Group B consists of patients who suffered mandibular fracture but were not subjected to exposure of Salmon Calcitonin nasal spray. The study was conducted from the period June 2023 to January 2025. The subjects were recruited as per the eligibility criteria after giving informed consent. The patients were randomly divided into two Groups for 18 months.

SELECTION CRITERIA

INCLUSION CRITERIA:

- Patients reported with an isolated unilateral Mandibular fracture.
- Patients within the age group of 16 to 60 years of both sexes.
- Patients who were willing to undergo the surgery.
- Patients who were ready to sign the written consent.
- Patients who were ready to comply with the follow-up protocol.

EXCLUSION CRITERIA:

- Patients with fractures to regions other than the mandible.
- Bony Pathologies or thyroid dysfunctions and ASA III, OR IV.
- Patients not willing to undergo the treatment.
- Patients not willing to participate in the study.
- Patients not ready for the follow-up.

PREOPERATIVE ASSESSMENT

- 2 ml of blood samples were collected from patients in both the study and control groups and later sent to the laboratory for plasma osteocalcin assessment.

SURGICAL PROTOCOL:

- The patients were operated on under GA/LA following a standardized aseptic surgical protocol after obtaining consent from the patients.
- The procedures were performed by the trained maxillofacial surgeons. Using armamentarium as shown in (Figure 1, 2).
- ORIF was carried out using a standardized surgical protocol. The fracture site was exposed, either intraorally or extraorally (based upon the fracture pattern).
- Fractured mandible was reduced to normal anatomical position and was fixed along Champy's line of osteosynthesis.
- Wound closure was performed using 3-0 vicryl sutures.
- None of the patients retained maxillomandibular fixation in the postoperative period.

POSTOPERATIVE MEDICATION:

- All the subjects (both study and control) were prescribed the same postoperative medications, including antibiotics and analgesics.

TEST GROUP: GROUP A

- Tablet Augmentin 625mg (Amoxycillin 500mg+Clavulanic acid125mg) twice a day for 7days
- Tablet Enzoflam (Paracetamol 325mg + Diclofenac 50mg + Seratiopeptidase 15mg) twice a day for 7days.
- Tablet Metrogyl (Metronidazole 500mg) twice a day for 7 days.
- Calcitonin nasal spray 200 IU (0.09 ml) in alternate nostrils once a day, along with 500mg calcium & 500 IU Vitamin D for 30 days
- Patients in the test group received intranasal salmon calcitonin. A dose of 200 IU (0.09 ml), one puff per day, was prescribed, along with 500 mg calcium (Shelcal) + 500 IU vitamin D (calcitriol 60,000IU/gm) / week for 30 postoperative days. The patients were instructed to administer the spray in alternate nostrils to avoid any nasal irritation. Each calcitonin spray bottle contained 3.7 ml of clear solution, with a concentration of 2200 IU salmon calcitonin per ml and 0.01% benzalkonium chloride as a preservative. In the event of any nasal irritation, patients should discontinue the spray immediately and report to the hospital. No calcitonin spray was administered to patients belonging to the control group.

CONTROL GROUP: GROUP B

- Tablet Augmentin 625mg (Amoxycillin 500mg+Clavulanic acid125mg) twice a day for 7 days.
- Tablet Enzoflam (Paracetamol 325mg+Diclofenac50mg+Seratopeptidase 15mg twice a day for 7 days.
- Tablet Metrogyl (Metronidazole 500mg) twice a day for 7 days.
- Along with 500 mg calcium (Shelcal) + 500 IU vitamin D (calcitriol 60,000IU/gm) / week for 30 postoperative days.

POST OPERATIVE PROCESSING OF BLOOD SAMPLE:

- After 30 days, 2 ml of postoperative blood sample were collected from both groups of patients and were sent for laboratory assessment of plasma

osteocalcin. The detection of plasma osteocalcin was performed using a sandwich ELISA technique.

FOLLOW UP:

- All patients underwent a standard postoperative assessment of clinical parameters, such as malocclusion, restricted mouth opening, step deformity and interfragmentary mobility. Complications such as swelling, pain, and paresthesia were also recorded.
- The evaluation criteria for this study included:
  - ✓ Postoperative pain assessment on 1^{st},3^{rd},7^{th} and 30^{th} day.
  - ✓ Biochemical assessment: osteocalcin comparison was done preoperative and on 30^{th} postoperative day & later was noted in ng/ml.
  - ✓ Radiological assessment : comparison was done preoperative and also on 30^{th} postoperative day
  - ✓ Postoperative complications were also noted.

EVALUATION CRITERIA:

- **Postoperative pain:** Pain was assessed postoperatively in both the study and control groups of patients using the VAS (visual analogue score) on 1^{st},$2^{nd,}$ $3^{rd,}$ $7^{th,}$ and 30^{th} postoperative days.
- **Biochemical assessment:** The levels of plasma osteocalcin, which is an indicator of osteoblastic activity, was also checked. Differences between preoperative and postoperative plasma osteocalcin samples (in ng/dl) were noted.
- **Radiological assessment:** OPG was used to assess fracture healing on the 4^{th}, 6^{th}, 8^{th} and 12th postoperative weeks. An absence of callus was given a score of 1, the presence of minimal callus a score of 2, a considerable amount of callus was scored 3, and complete fusion of the fracture will imply a score of 4 (Aswath G, Elavenil P, Thulasi DG et al., 2020).[51]

ARMAMENTARIUM

Figure 1: ORIF Armamentarium.

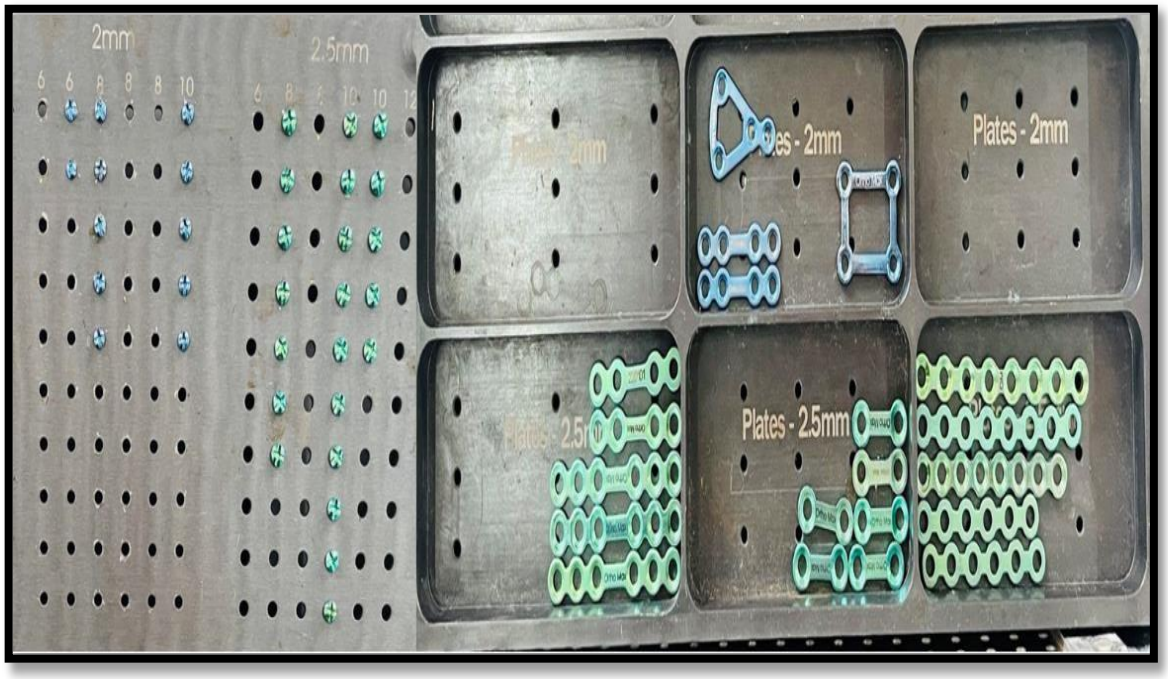


Figure 2: Implants used in ORIF- Titanium plates & titanium screw

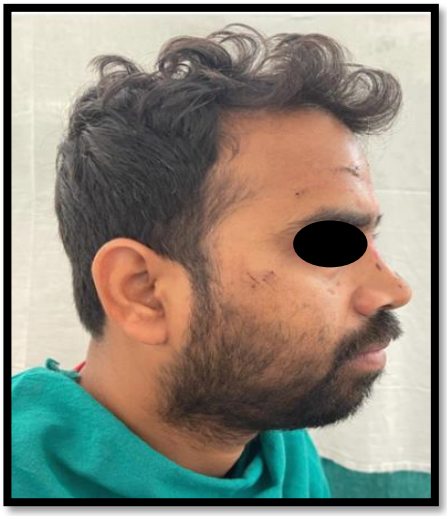
Statistical Analysis

- All statistical analyses for the present study were performed using IBM SPSS Statistics for Windows, Version 25.0 (Armonk, NY: IBM Corp.).
- Descriptive statistics were used to summarize the demographic and clinical characteristics of the participants.
- Continuous variables such as serum osteocalcin levels and pain scores (VAS) were expressed as mean ± standard deviation (SD) along with range, while categorical variables (e.g., Moed radiographic healing scores and site distribution) were expressed in terms of frequency and percentage.
- The normality of the distribution of continuous variables was assessed using the Shapiro–Wilk test. Since most variables did not follow a normal distribution, non-parametric tests were employed for statistical comparisons.
- Between-group comparisons for continuous variables (e.g., osteocalcin levels and VAS scores) were analyzed using the Mann–Whitney U test, and between-group comparisons for categorical variables (e.g., Moed scoring levels, complication rates) were conducted using the Fisher's Exact test due to the small sample size and expected cell counts below five.
- Within-group comparisons (preoperative vs. postoperative osteocalcin levels) were performed using the Wilcoxon Signed Ranks test, a non-parametric alternative to the paired t-test, to evaluate the significance of change over time.
- For all analyses, a p-value less than 0.05 ($p < 0.05$) was considered to indicate statistical significance.

REPRESENTATIVE CASES

a.

b.



c.

Figure 3.1: Pre-operative profile a. Frontal b. Left lateral c. Right lateral

a.

b.

c.

Figure 3.2: Pre-operative occlusion a. Right lateral b. Left lateral c. Frontal

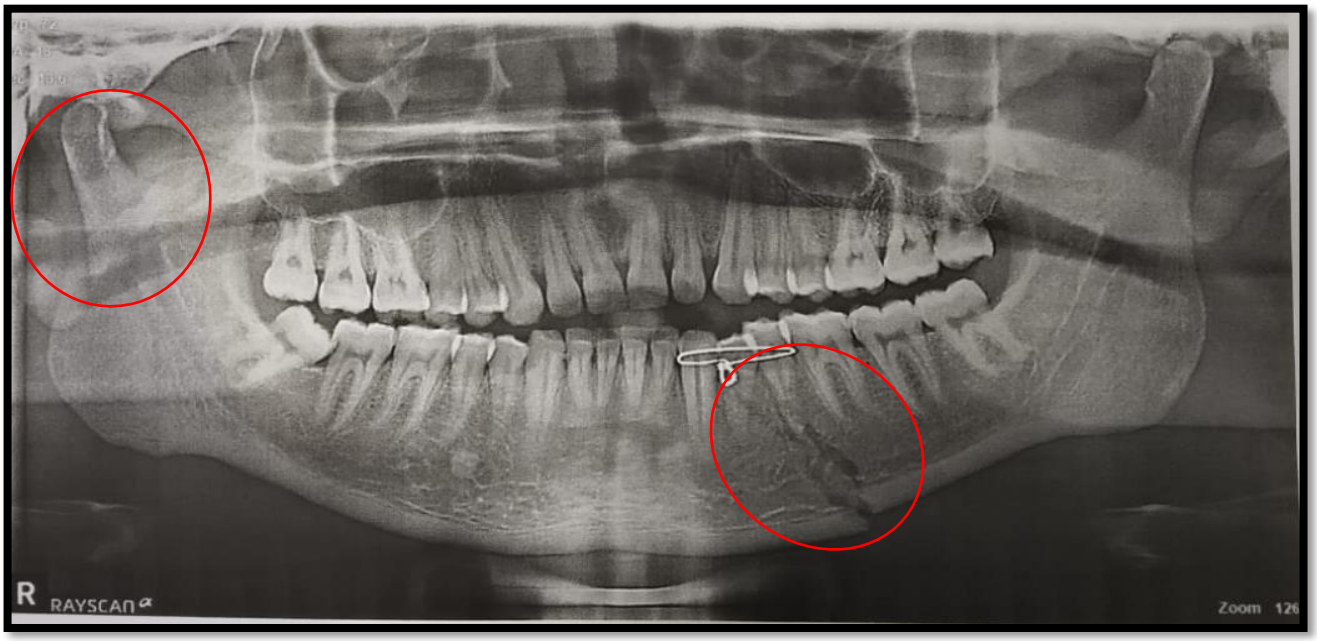


Figure 3.3 Pre-operative OPG

Medical Laboratory Report

220054000292766

Mr. CHANDAN JHA 7737054707
HEALTHIANS, INDUSTRIAL COMPLEX DUNDAH
Tel No : 9999999999
PIN No: 122016
PID NO: P542200313174
Age: 38.0 Year(s) Sex: Male

Reference: Dr.SELF
Sample Collected At:
Expedient Healthcare Marketing Private Limited
Plot No.518, Udyog Vihar, Phase-iii, Gurgaon, Haryana, 122016
Processing Location:- Metropolis Healthcare Ltd,unit No409-416,4th Floor,commercial Building-1,kohinoor Mall,mumbai-70

VID: 220054000292766
Registered On:
28/03/2023 06:19 PM
Collected On:
28/03/2023 6:20PM
Reported On:
29/03/2023 04:59 PM

Investigation	Observed Value	Unit	Biological Reference Interval
Osteocalcin BGP-Bone Gla Protein (Serum,CLIA)	16.5	ng/mL	4.6-65.4

Interpretation :

1. Elevated osteocalcin occurs in osteomalacia, Pagets disease of bone, healing fracture, osteogenic sarcoma, adequate therapy for osteoporosis, primary hyperthyroidism, renal osteodystrophy and post menopausal osteoporosis.
2. Decreased levels are seen in hypoparathyroidism, Cushings syndrome and long term corticosteroid therapy.
3. Bone markers are used to monitor therapy for bone disease and to judge response to anti-resorption or bone formation therapies in a much shorter time period than the X-ray types of bone density testing.

-- End of Report --

Figure 3.4 Pre-operative Serum Osteocalcin levels

a. b.

c.

Figure 3.5: Intra-operative occlusion a. Right lateral b. Left lateral c. Frontal

a. b.

Figure 3.6: a. Surface marking b. Retro mandibular incision.

Figure 3.7: Exposure of fracture site

Figure 3.8: Reduction of fracture site

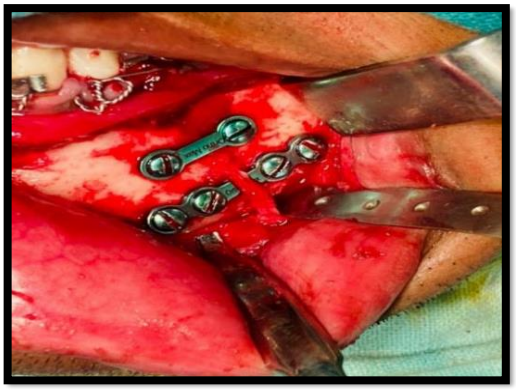


Figure 3.9: Fixation of fracture site

Figure 3.10: Closure

Figure 3.11 Exposure of condylar fracture site

Figure 3.12: Reduction of fracture site

Figure 3.13: Fixation of fracture site

Figure 3.14: Closure

a. b.

c.

Figure 3.15: Post-operative occlusion a. Left lateral b. Right lateral c. Frontal

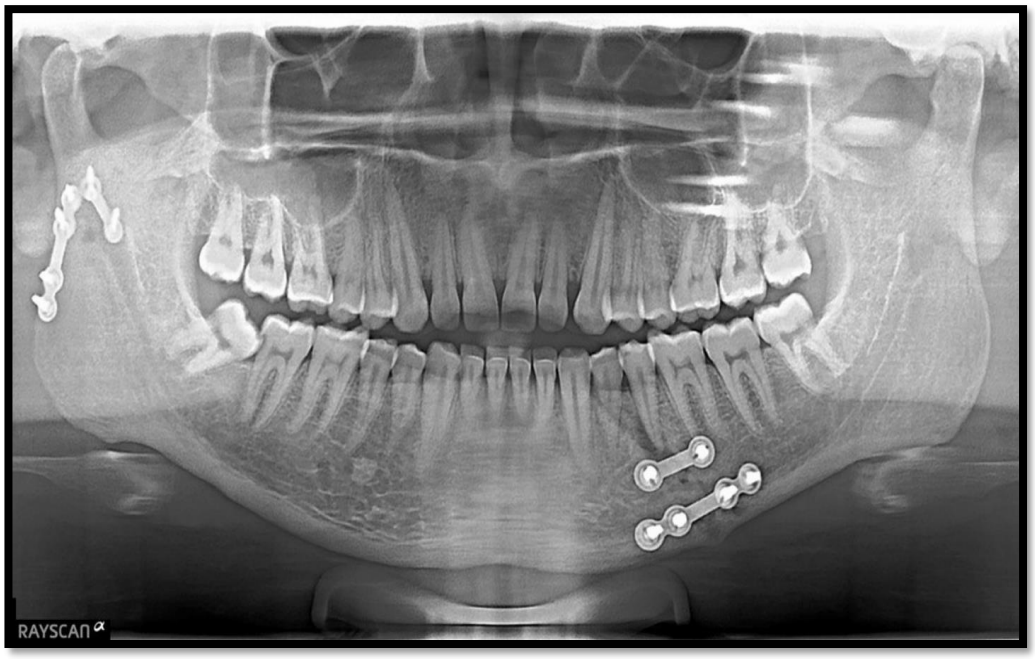
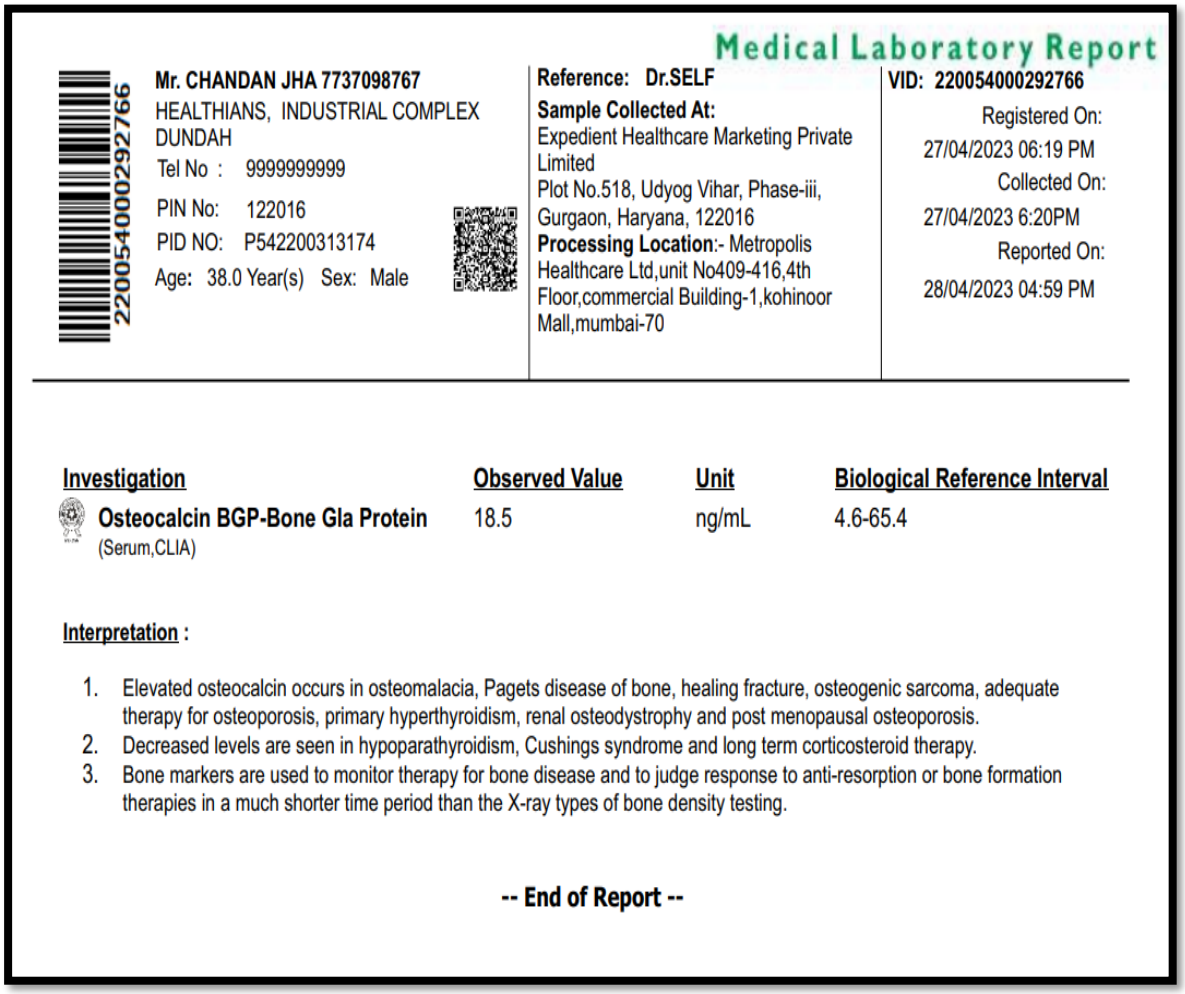


Figure 3.16: 1 Month Post-operative OPG



Medical Laboratory Report

2200540002927766

Mr. CHANDAN JHA 7737098767
HEALTHIANS, INDUSTRIAL COMPLEX
DUNDAH
Tel No : 9999999999
PIN No: 122016
PID NO: P542200313174
Age: 38.0 Year(s) Sex: Male

Reference: Dr.SELF
Sample Collected At:
Expedient Healthcare Marketing Private Limited
Plot No.518, Udyog Vihar, Phase-iii, Gurgaon, Haryana, 122016
Processing Location:- Metropolis Healthcare Ltd,unit No409-416,4th Floor,commercial Building-1,kohinoor Mall,mumbai-70

VID: 220054000292766
Registered On:
27/04/2023 06:19 PM
Collected On:
27/04/2023 6:20PM
Reported On:
28/04/2023 04:59 PM

Investigation	Observed Value	Unit	Biological Reference Interval
Osteocalcin BGP-Bone Gla Protein (Serum,CLIA)	18.5	ng/mL	4.6-65.4

Interpretation :

1. Elevated osteocalcin occurs in osteomalacia, Pagets disease of bone, healing fracture, osteogenic sarcoma, adequate therapy for osteoporosis, primary hyperthyroidism, renal osteodystrophy and post menopausal osteoporosis.
2. Decreased levels are seen in hypoparathyroidism, Cushings syndrome and long term corticosteroid therapy.
3. Bone markers are used to monitor therapy for bone disease and to judge response to anti-resorption or bone formation therapies in a much shorter time period than the X-ray types of bone density testing.

-- End of Report --

Figure 3.17: Post-operative serum osteocalcin

GROUP B

a

b

c

Figure 4.1: Pre-operative profile a. Frontal b. Left lateral c. Right lateral

a.

b.

c.

Figure 4.2: Pre-operative occlusion a. Right lateral b. Left lateral c. Frontal

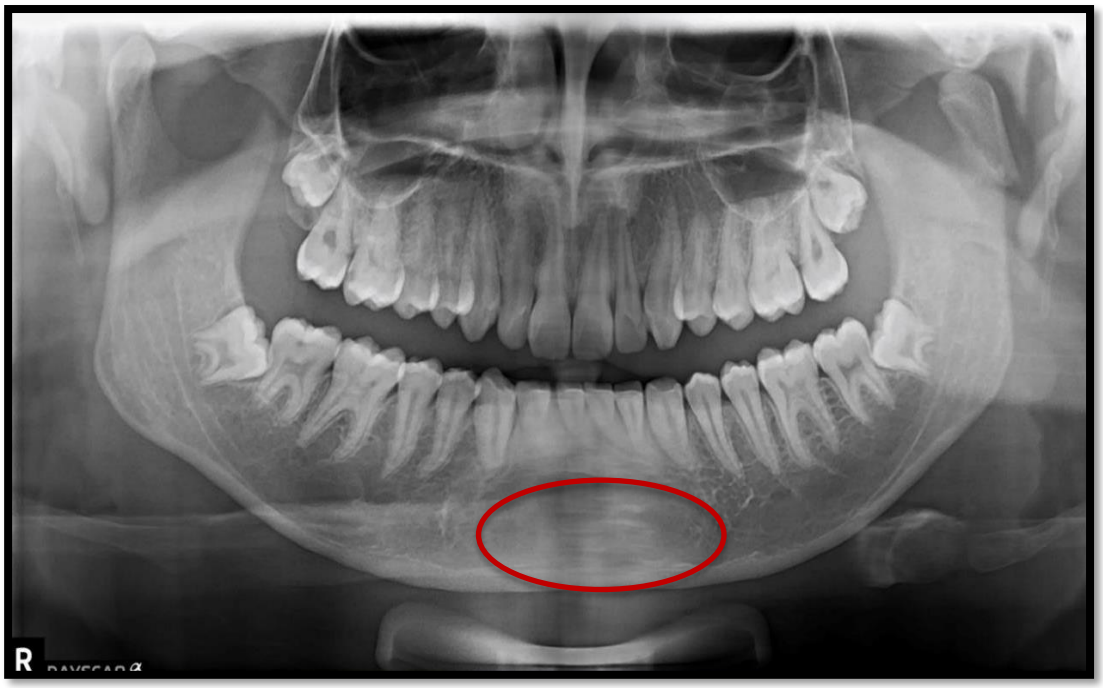
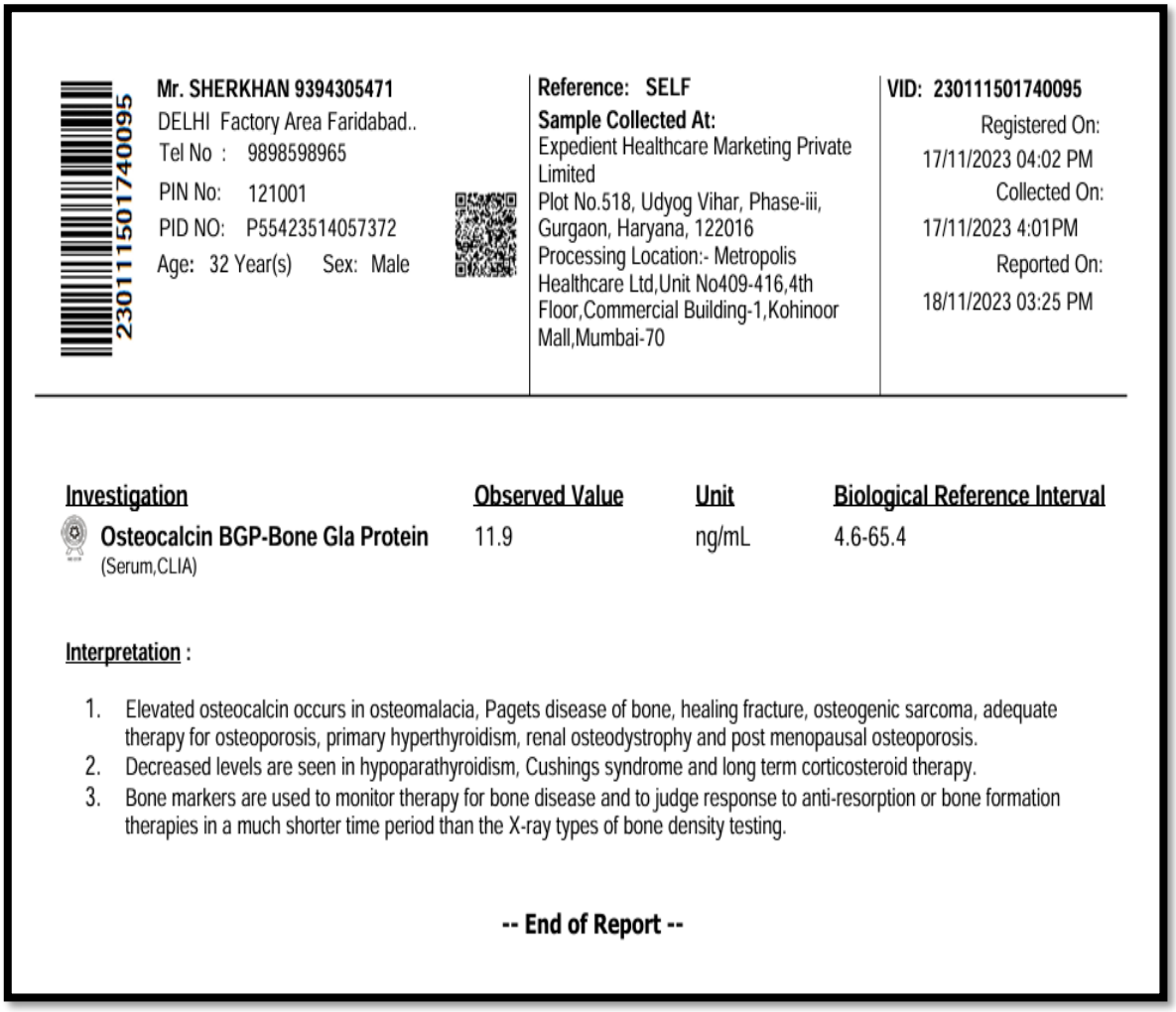


Figure 4.3 Pre-operative OPG



Mr. SHERKHAN 9394305471
DELHI Factory Area Faridabad..
Tel No : 9898598965
PIN No: 121001
PID NO: P55423514057372
Age: 32 Year(s) Sex: Male

Reference: SELF
Sample Collected At:
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Plot No.518, Udyog Vihar, Phase-iii, Gurgaon, Haryana, 122016
Processing Location:- Metropolis Healthcare Ltd,Unit No409-416,4th Floor,Commercial Building-1,Kohinoor Mall,Mumbai-70

VID: 230111501740095
Registered On: 17/11/2023 04:02 PM
Collected On: 17/11/2023 4:01PM
Reported On: 18/11/2023 03:25 PM

Investigation	Observed Value	Unit	Biological Reference Interval
Osteocalcin BGP-Bone Gla Protein (Serum,CLIA)	11.9	ng/mL	4.6-65.4

Interpretation :

1. Elevated osteocalcin occurs in osteomalacia, Pagets disease of bone, healing fracture, osteogenic sarcoma, adequate therapy for osteoporosis, primary hyperthyroidism, renal osteodystrophy and post menopausal osteoporosis.
2. Decreased levels are seen in hypoparathyroidism, Cushings syndrome and long term corticosteroid therapy.
3. Bone markers are used to monitor therapy for bone disease and to judge response to anti-resorption or bone formation therapies in a much shorter time period than the X-ray types of bone density testing.

-- End of Report --

Figure 4.4: Pre- operative Serum Osteocalcin levels

a.

b.

c.

Figure 4.5: Intraoperative occlusion a. Right lateral b. Left lateral. c. Frontal

Figure 4.6: Surface marking for vestibular incison

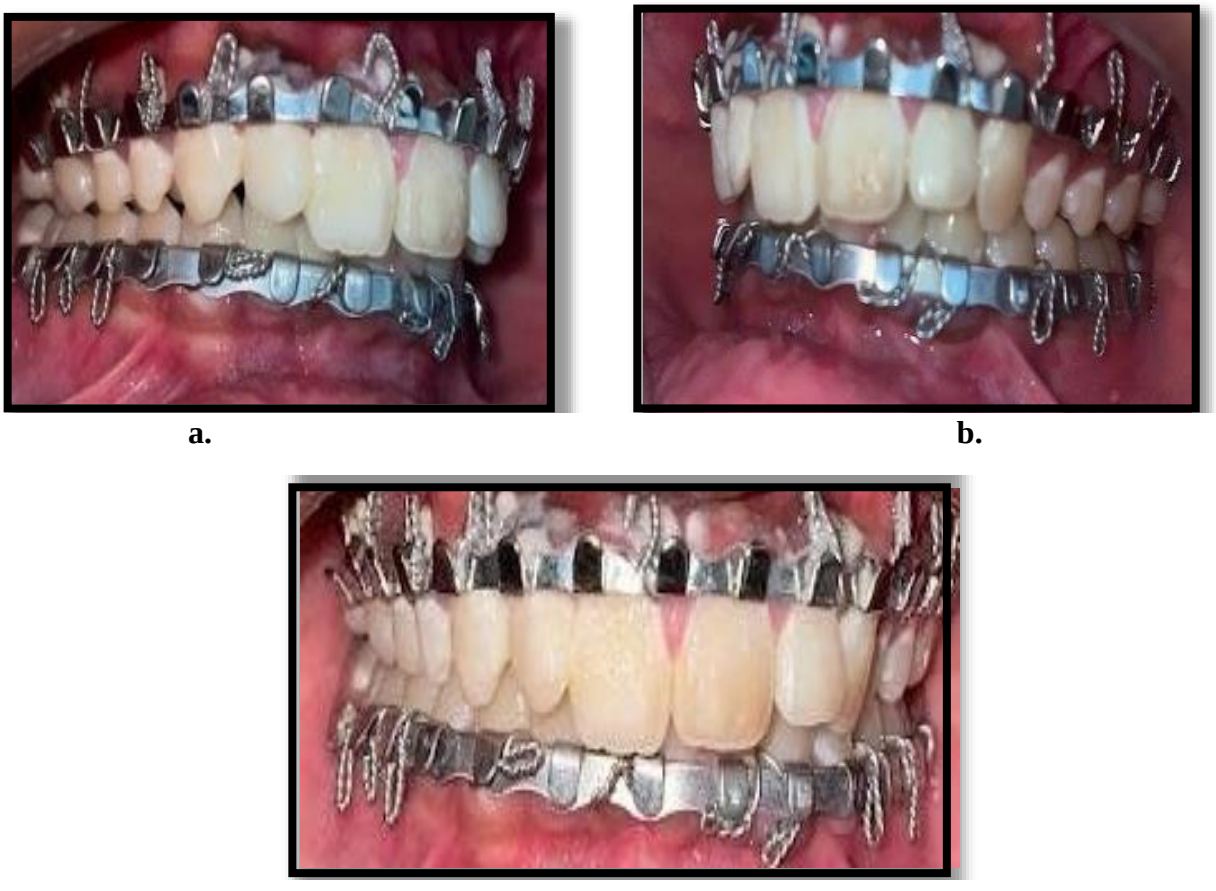
Figure 4.7. Exposure of the fracture site

Figure 4.8: Reduction of fracture

Figure 4.9: Fixation of fracture

Figure 4.10: Closure

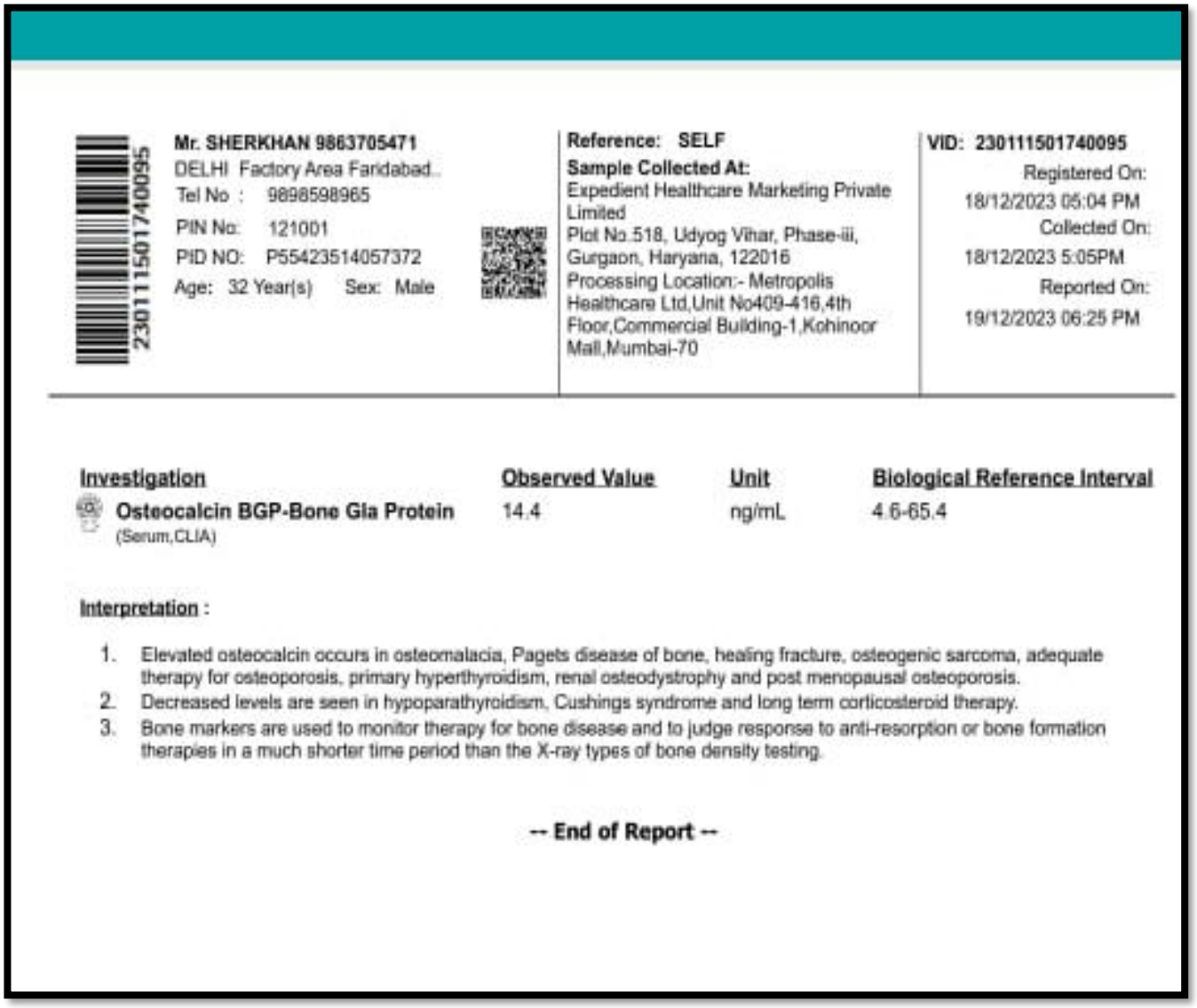
Figure 4.11: 1 Month Post-operative OPG



a. **b.**

c.

Figure 4.12: Post-operative occlusion a. Right lateral b. Left lateral. c. Frontal



Mr. SHERKHAN 9863705471
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Tel No : 9898598965
PIN No: 121001
PID NO: P55423514057372
Age: 32 Year(s) Sex: Male

230111501740095

Reference: SELF
Sample Collected At:
Expedient Healthcare Marketing Private Limited
Plot No.518, Udyog Vihar, Phase-iii, Gurgaon, Haryana, 122016
Processing Location:- Metropolis Healthcare Ltd,Unit No409-416,4th Floor,Commercial Building-1,Kohinoor Mall,Mumbai-70

VID: 230111501740095
Registered On: 18/12/2023 05:04 PM
Collected On: 18/12/2023 5:05PM
Reported On: 19/12/2023 06:25 PM

Investigation	Observed Value	Unit	Biological Reference Interval
Osteocalcin BGP-Bone Gla Protein (Serum,CLIA)	14.4	ng/mL	4.6-65.4

Interpretation :

1. Elevated osteocalcin occurs in osteomalacia, Pagets disease of bone, healing fracture, osteogenic sarcoma, adequate therapy for osteoporosis, primary hyperthyroidism, renal osteodystrophy and post menopausal osteoporosis.
2. Decreased levels are seen in hypoparathyroidism, Cushings syndrome and long term corticosteroid therapy.
3. Bone markers are used to monitor therapy for bone disease and to judge response to anti-resorption or bone formation therapies in a much shorter time period than the X-ray types of bone density testing.

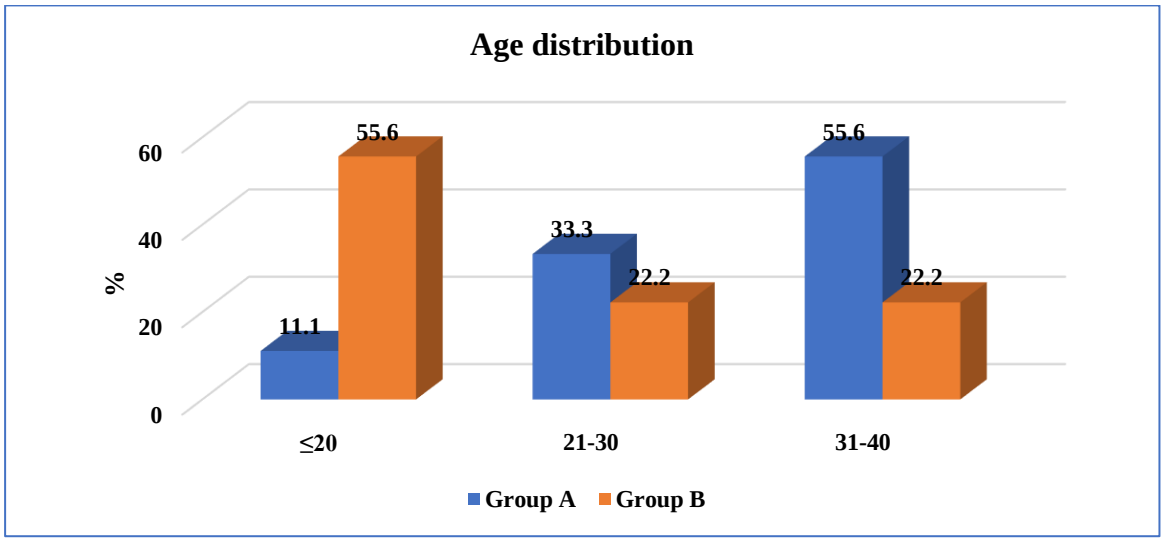
-- End of Report --

Figure 4.13: Post-operative serum osteocalcin levels

RESULTS

Age	Group A n(%)	Group B n(%)	Mann Whitney U	P value
≤20	1(11.1)	5(55.6)		
21-30	3(33.3)	2(22.2)		
31-40	5(55.6)	2(22.2)		
Total	9(100)	9(100)		
Range	19-37	17-38		
Mean ± SD	39.17 ± 14.13	33.33 ± 12.64	22	0.100

Table 1: Age Distribution (Years)



Graph 1: Age Distribution (Years)

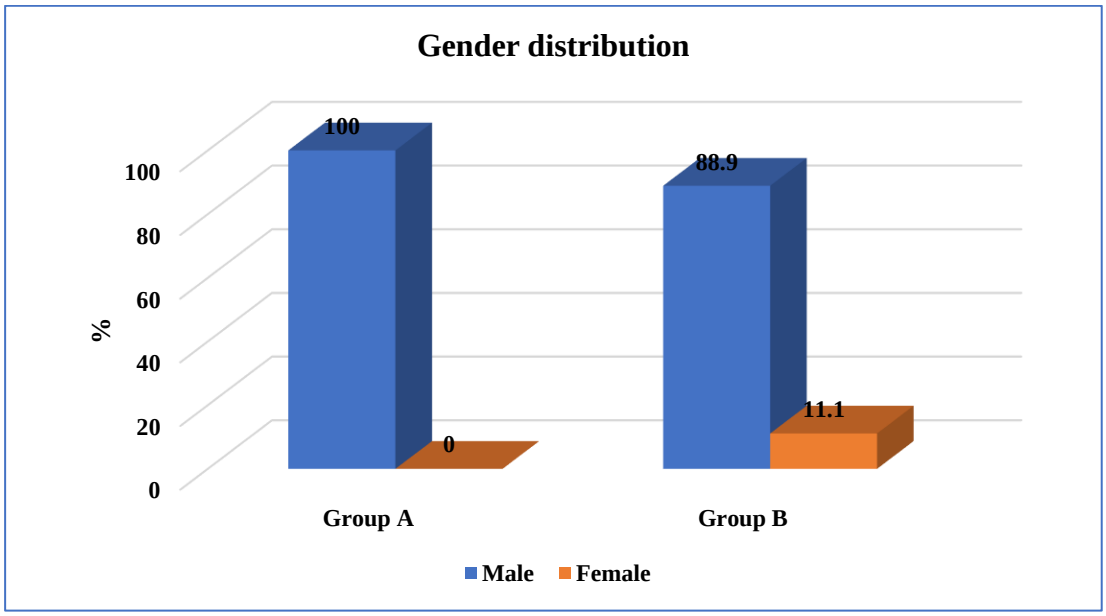
Observation

The age distribution of patients in Group A and Group B was analyzed in Table 1 & Graph 1 using the Mann–Whitney U test. In the ≤20 years age group, 1 patient (11.1%) was observed in Group A, while a significantly higher number, 5 patients (55.6%), was noted in Group B, indicating a relatively younger cohort in Group B. In the 21–30 years age group, 3 patients (33.3%) belonged to Group A and 2 patients (22.2%) to Group B. The 31–40 years age group included 5 patients (55.6%) in Group A and 2 patients (22.2%) in Group B, suggesting a more adult-age skew in

Group A compared to Group B. The total number of patients in each group was equal (n = 9), maintaining a balanced sample size. The age range in Group A was 19 to 37 years, and in Group B, it was slightly broader, ranging from 17 to 38 years. The mean age ± standard deviation was 39.17 ± 14.13 years in Group A and 33.33 ± 12.64 years in Group B. The Mann–Whitney U value was 22, and the associated p-value was 0.100, indicating that the difference was not statistically significant (p > 0.05).

Gender	Group A n(%)	Group B n(%)	P value
Male	9(100)	8(88.9)	0.99
Female	0	1(11.1)	
Total	9(100)	9(100)	

Table 2: Gender Distribution (Fisher's Exact test)



Graph 2: Gender Distribution

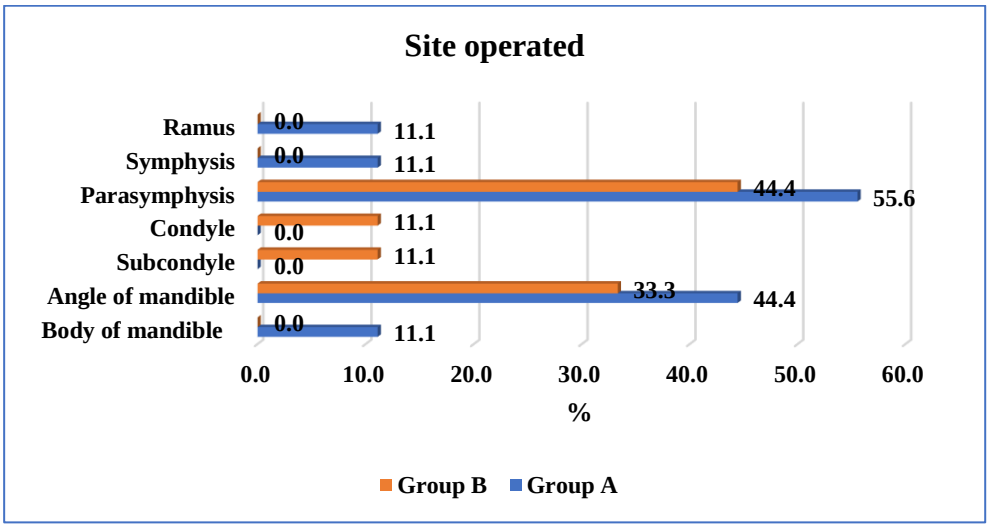
Observation

Due to small sample size in Table 2 and Graph 2, the gender distribution of patients in Group A and Group B was compared using Fisher's Exact test. There were no female patients (0%) in Group A, and all 9 patients (100%) were male. Eight patients (88.9%) and one patient (11.1%) were male and female, respectively, in

Group B. To ensure sample size comparability, each group had the same total number of participants (n = 9 per group). The comparison generated a p-value of 0.99, i.e. not statistically significant (p > 0.05).

Site	Group A n(%)	Group B n(%)	P value
Body of mandible	1(11.1)	0	0.553
Angle of mandible	4(44.4)	3(33.3)	
Subcondyle	0	1(11.1)	
Condyle	0	1(11.1)	
Parasymphysis	5(55.6)	4(44.4)	
Symphysis	1(11.1)	0	
Ramus	1(11.1)	0	

Table 3: Site operated (Fisher Exact test)



Graph 3: Site operated

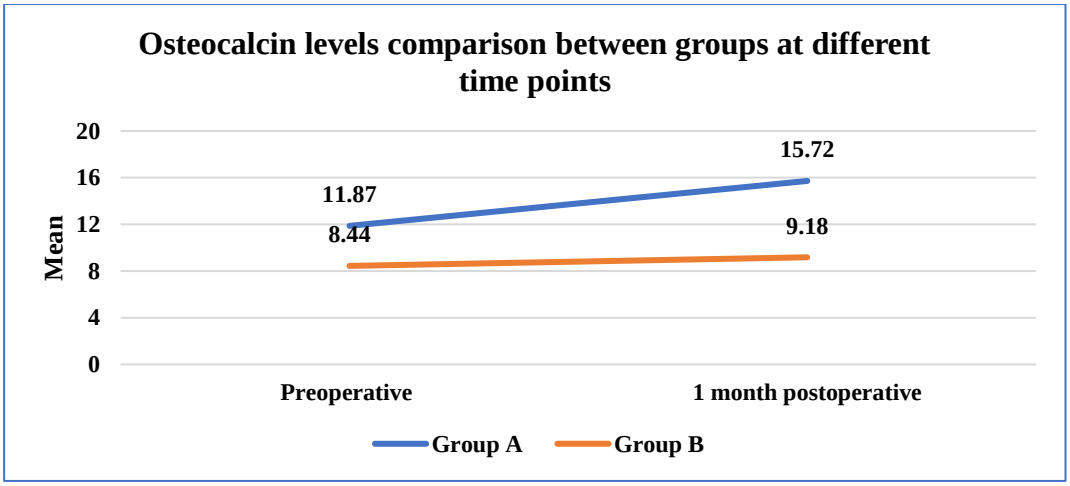
Observation

The distribution of fracture sites operated in Group A and Group B was analyzed using Fisher's Exact test. As per Table 3 and Graph 3: Group A, the most frequently involved site was the parasymphysis region, observed in 5 patients (55.6%), followed by the angle of the mandible in 4 patients (44.4%). Other anatomical sites operated in Group A included the body of the mandible (1 patient; 11.1%), symphysis (1 patient; 11.1%), and ramus (1 patient; 11.1%).

In Group B, the parasymphysis (4 patients; 44.4%) and angle of the mandible (3 patients; 33.3%) were also the most involved regions. Additionally, 1 patient (11.1%) each in Group B had fractures involving the sub condyle and condyle regions, which were not observed in Group A. Notably, no patients in Group B had fractures involving the body of the mandible, symphysis, or ramus regions. The p-value obtained from Fisher's Exact test was 0.553, indicating that there was no statistically significant difference. Thus, both groups demonstrated a comparable pattern regarding the anatomical site distribution of mandibular fractures.

Osteocalcin levels	**Group A** (Mean ± SD)	**Group B** (Mean ± SD)	**Mann Whitney U**	**P value**
Preoperative	11.87 ± 9.72	8.44 ± 5.29	36.50	0.724
1 month postoperative	15.72 ± 9.08	9.18 ± 5.70	19	0.063
Difference	3.84 ± 3.28	0.74 ± 0.58	7.50	0.002*

Table 4: Osteocalcin levels (nanograms per milliliter) comparison between groups at different time points *statistically significant p<0.05, Mann-Whitney U test



Graph 4: Osteocalcin levels (nanograms per milliliter) comparison between groups at different time points

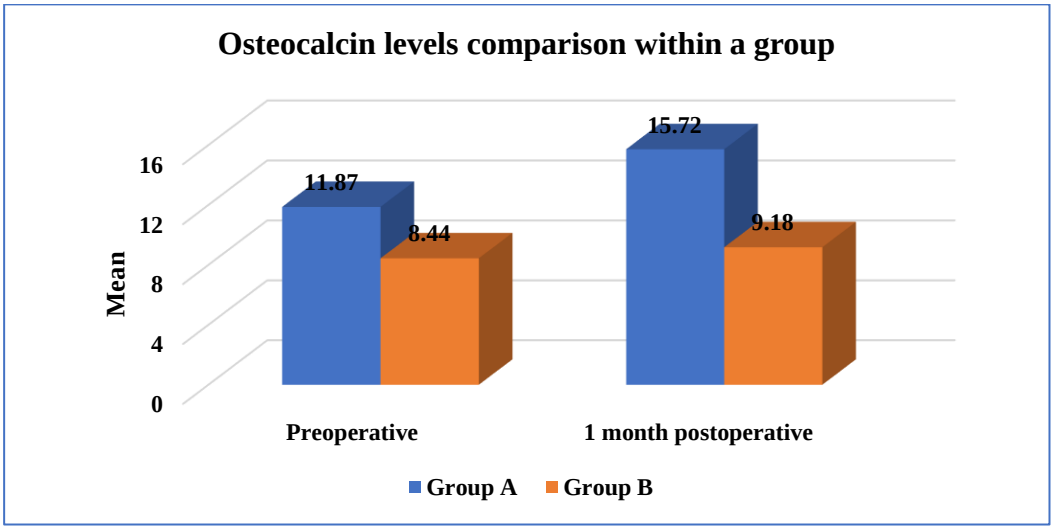
Observation

The biochemical comparison of serum osteocalcin levels (in ng/dl) between the control and study groups was analyzed in Table 4 and Graph 4, preoperatively and postoperatively.

- Preoperative osteocalcin levels were slightly higher in the Study Group (mean ≈ 11.87 ± 9.72) compared to the Control Group (mean ≈ 8.44 ± 5.29), indicating a minor baseline difference in osteoblastic activity. However, this difference was not statistically significant.
- Postoperative osteocalcin levels showed a considerable increase in the Study Group (mean ≈ 15.72 ± 9.08). In contrast, the Control Group showed only a marginal rise (mean ≈ 9.18 ± 5.70), indicating enhanced osteoblastic activity and bone formation in the Study Group receiving intranasal salmon calcitonin nasal spray.
- The Study Group had a substantially larger mean difference (postoperative - preoperative) in osteocalcin levels compared to the Control Group (mean difference = 3.84 ± 3.28 vs. 0.74 ± 0.58).
- Calcitonin nasal spray significantly improved bone healing markers in individuals with mandibular fractures following ORIF (p-value = 0.002).

Osteocalcin levels	**Group A**	**Group B**
Preoperative	11.87 ± 9.72	8.44 ± 5.29
1 month postoperative	15.72 ± 9.08	9.18 ± 5.70
Z	2.666	2.666
P value	0.008*	0.008*

Table 5: Osteocalcin levels (nanograms per milliliter) comparison within a group (Intragroup analysis) *statistically significant $p<0.05$, Wilcoxon Signed Rank test



Graph 5: Osteocalcin levels (nanograms per milliliter) comparison within a group (Intragroup analysis)

Observation

The intragroup comparison in Table 5 and Graph 5 of serum osteocalcin levels (in nanograms per milliliter) was conducted within both Group A and Group B, assessing the biochemical changes from preoperative to one-month postoperative period using the Wilcoxon Signed Rank test.

In Group A, the mean preoperative osteocalcin level was 11.87 ± 9.72 ng/ml, which increased to 15.72 ± 9.08 ng/ml one month postoperatively. This rise in osteocalcin levels indicates a significant increase in osteoblastic activity and bone turnover, suggesting enhanced bone healing in patients who received salmon calcitonin nasal spray. The statistical analysis showed a Z value of 2.666, with a p-value of 0.008, indicating a statistically significant difference ($p < 0.05$) in osteocalcin levels within Group A.

Similarly, in Group B, the mean preoperative osteocalcin level was 8.44 ± 5.29 ng/ml, which increased slightly to 9.18 ± 5.70 ng/ml at the one-month postoperative follow-up. Although this also represents an improvement, the degree of change was relatively modest compared to Group A. Nonetheless, the Z value of 2.666 and p-value of 0.008 indicate that the change was also statistically significant ($p < 0.05$) within Group B.

Overall, both groups showed significant increases in osteocalcin levels over time; however, the magnitude of biochemical improvement was more pronounced in Group A, reinforcing the efficacy of intranasal salmon calcitonin spray as a bone mineralizing agent.

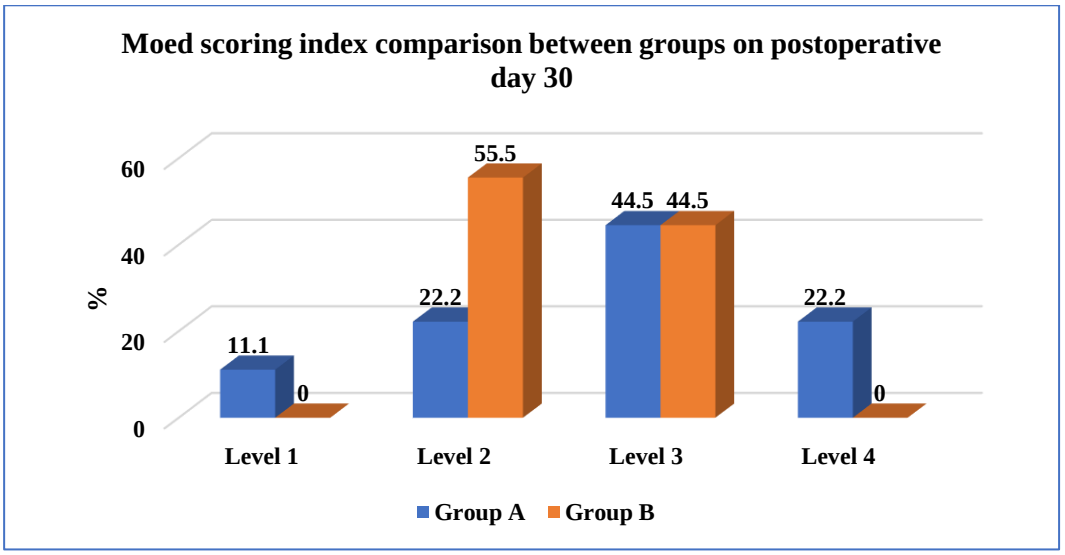
Level	Group A n(%)	Group B n(%)	P value
Level 1	1(11.1)	0	0.278
Level 2	2(22.2)	5(55.5)	
Level 3	4(44.5)	4(44.5)	
Level 4	2(22.2)	0	
Total	9(100)	9(100)	

Table 6: Moed scoring index comparison between groups at postoperative Day 30

Fisher Exact test

Where,

- Level I: 1mm hyperechoic with no callus, clear fracture gap, and slightly fuzzy boundaries at the fracture ends.
- Level II: 0.5-0.7mm hypoechoic with few calluses and an obscure but still existent fracture gap.
- Level III: 3 points for more calluses and an obscure but still existent fracture gap.
- Level IV: indistinct fracture gap, large number of calluses, and completely connected fracture ends.



Graph 6: Moed scoring index comparison between groups on postoperative Day 30

Observation

The radiological assessment of fracture healing between Group A and Group B on postoperative day 30 was evaluated using the Moed Scoring Index. In Group A, 1 patient (11.1%) was categorized as Level I, indicating minimal healing with no callus formation and a clear fracture gap. Two patients (22.2%) were assessed at Level II, representing few calluses and a still-visible fracture gap. The majority of patients in Group A demonstrated better healing outcomes, with 4 patients (44.4%) scoring Level III, denoting more callus formation and obscure but persistent fracture gap, and 2 patients (22.2%) achieving Level IV, which signifies indistinct fracture gap and complete union with abundant callus formation.

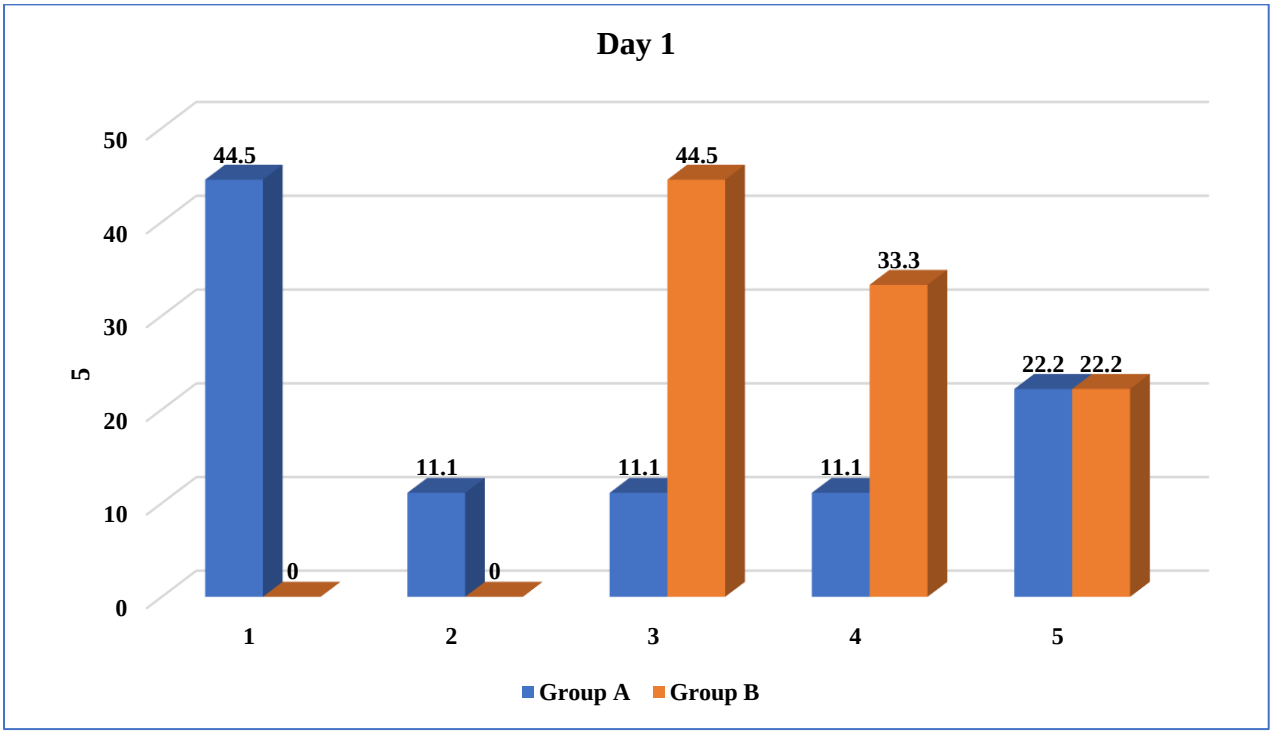
In contrast, in Group B, no patients (0%) were found in Level I or Level IV categories. Five patients (55.5%) were scored at Level II, indicating slower healing with minimal callus formation, while four patients (44.4%) were scored at Level III, similar to Group A. The comparison between the two groups yielded a p-value of 0.278, indicating that the it was not statistically significant ($p > 0.05$). However, a clinically favorable trend toward higher healing levels (Level IV) was observed in Group A, suggesting better radiological bone healing in patients receiving salmon calcitonin nasal spray.

Level	Group A n(%)	Group B n(%)	P value
Day 1			
1	4(44.5)	0	0.109
2	1(11.1)	0	
3	1(11.1)	4(44.5)	
4	1(11.1)	3(33.3)	
5	2(22.2)	2(22.2)	
Day 3			
0	0	4(44.5)	0.136
2	6(66.7)	3(33.3)	
3	3(33.3)	2(22.2)	
Day 7			
0	5(55.6)	5(55.6)	0.99
1	3(33.3)	3(33.3)	
2	1(11.1)	1(11.1)	
Day 30			
0	8(88.9)	7(77.8)	0.99
1	1(11.1)	2(22.2)	

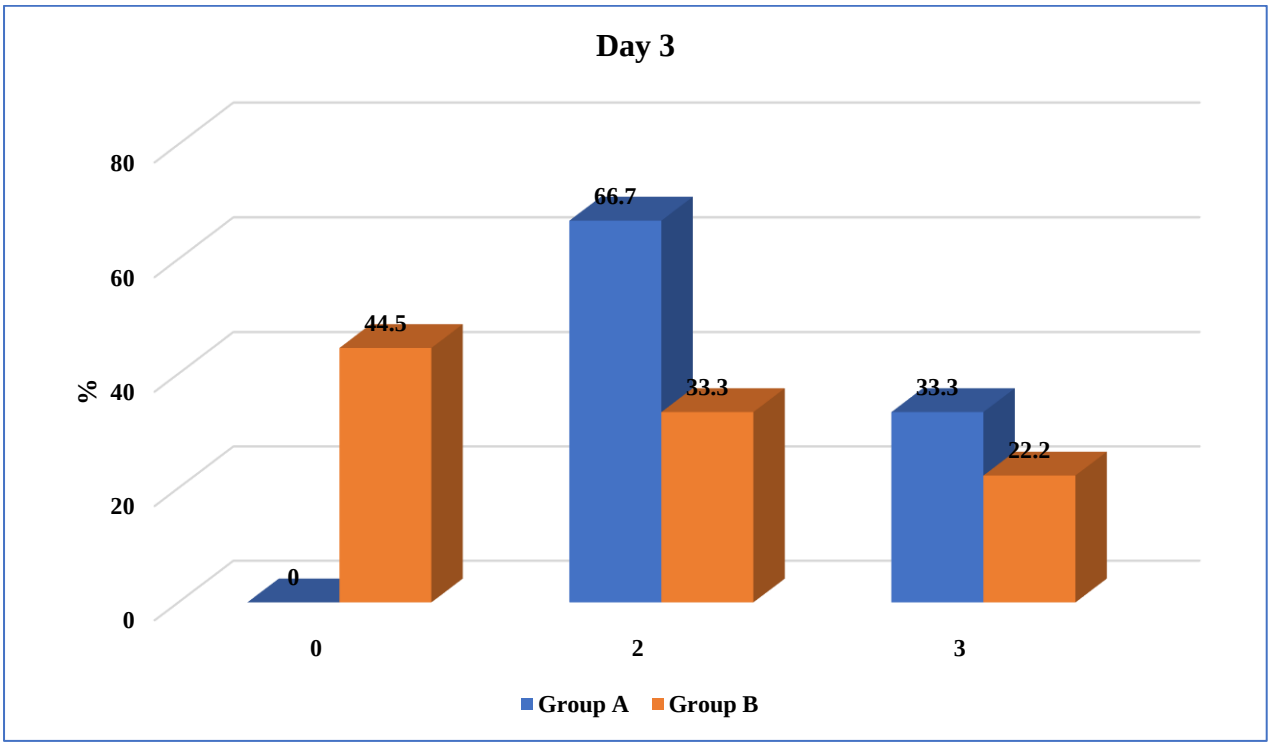
Table 7: VAS Score comparison between groups on postoperative days 1, 3, 7, and 30

Fisher Exact test

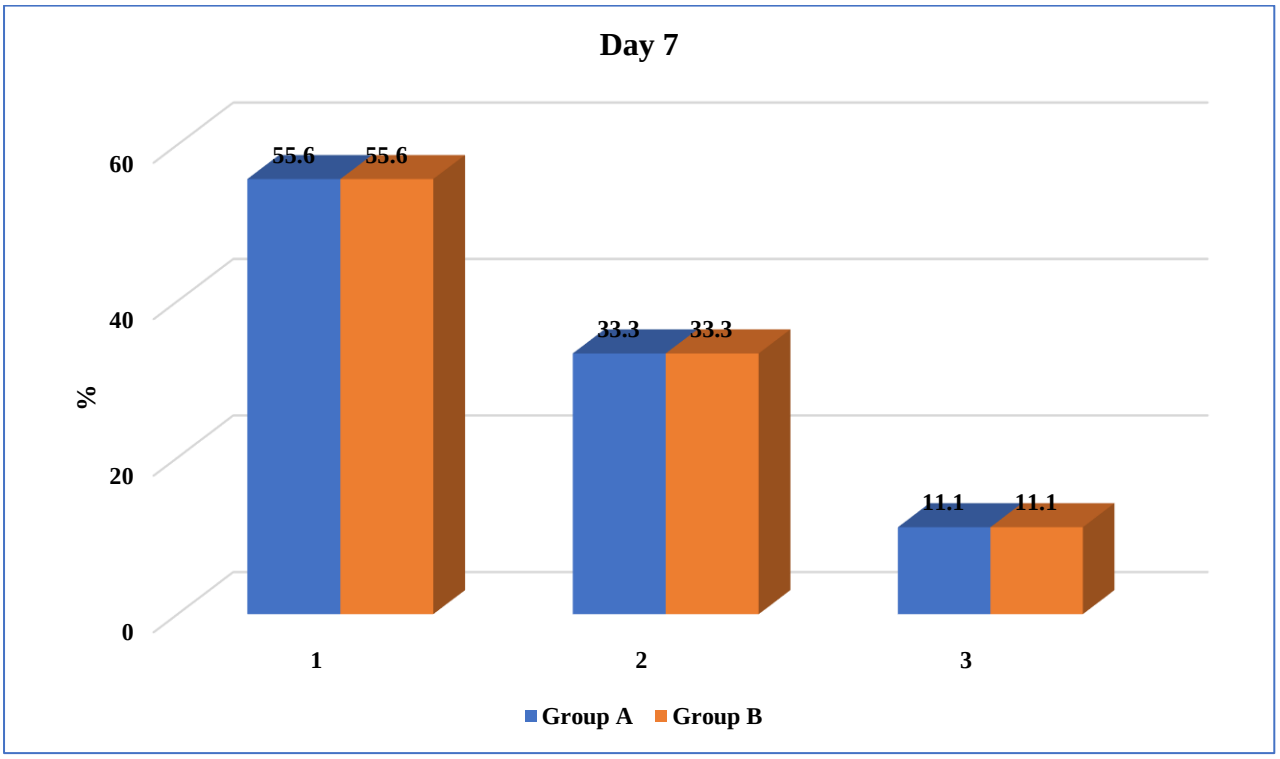
Where, V1: No Pain; V2: Mild Pain; V3: Moderate Pain; V4: Severe Pain; V5: Worst Pain Possible



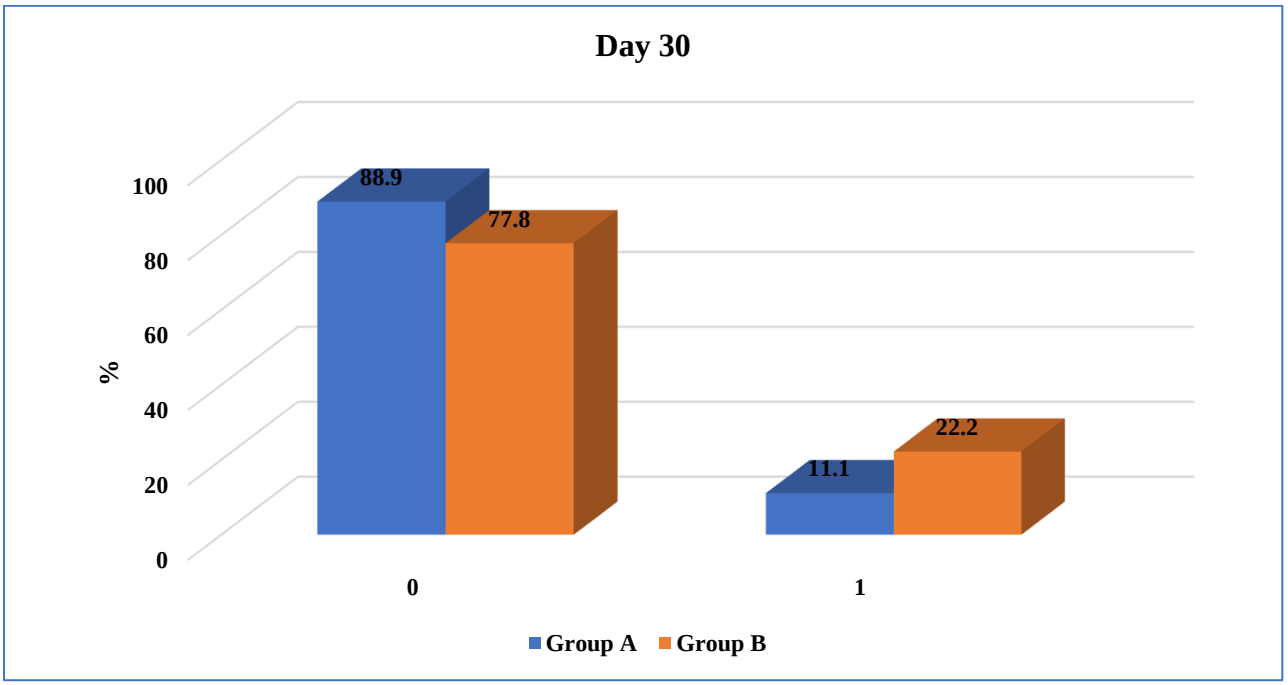
Graph 7a: VAS Score comparison between groups on postoperative Day 1



Graph 7b: VAS Score comparison between groups on postoperative day 3



Graph 7c: VAS Score comparison between groups on postoperative day 7



Graph 7d: VAS Score comparison between groups on postoperative day 30

Observation

Postoperative pain intensity was assessed and compared between Group A and Group B using VAS on postoperative days 1, 3, 7, and 30. The same is represented in Table 7, Graphs 7a, 7b, 7c, 7d.

On postoperative day 1, Group A demonstrated a greater number of patients reporting lower VAS scores, with 4 patients (44.5%) experiencing only mild pain (VAS 1), and 1 patient (11.1%) each in VAS scores 2, 3, and 4, and 2 patients (22.2%) reporting worst pain (VAS 5). In contrast, Group B showed a more varied and moderate pain distribution, with no patients (0%) in VAS 1 or 2, 4 patients (44.5%) reporting moderate pain (VAS 3), 3 patients (33.3%) reporting severe pain (VAS 4), and 2 patients (22.2%) experiencing worst pain (VAS 5). The p-value was 0.109, suggesting no statistically significant difference in pain scores between groups on Day 1, although clinically better pain control was evident in Group A.

On day 3, Group B showed a shift toward improvement, with 4 patients (44.5%) being pain-free (VAS 0), whereas none in Group A (0%) reported VAS 0 at this time. However, 66.7% (6 patients) in Group A had mild pain (VAS 2), and the remaining 3 patients (33.3%) had moderate pain (VAS 3), indicating steady pain reduction. In Group B, 3 patients (33.3%) had mild pain (VAS 2) and 2 patients (22.2%) had moderate pain (VAS 3). The p-value was 0.136, again showing no statistical significance, but with clinical improvement in both groups.

By postoperative day 7, pain relief had markedly improved in both groups, with 5 patients (55.6%) in each group being pain-free (VAS 0), 3 patients (33.3%) reporting mild pain (VAS 1), and 1 patient (11.1%) reporting VAS 2 in both groups. The p-value was 0.99, indicating no significant difference between the groups.

On day 30, almost complete pain resolution was observed in both groups. 8 patients (88.9%) in Group A and 7 patients (77.8%) in Group B were pain-free (VAS 0), and only 1 patient (11.1%) in Group A and 2 patients (22.2%) in Group B reported mild residual pain (VAS 1). The comparison yielded a p-value of 0.99, showing no significant difference in pain levels at the final follow-up.Overall, although the differences in VAS scores between the groups at different time points were not statistically significant, a clinically observable trend toward better early postoperative pain control was evident in Group A (Calcitonin group) compared to the control group.

Overall Summary of Results (Tables 1 to 7)

The results of this prospective clinical study were analyzed based on demographic, clinical, biochemical, radiographic, and pain-related parameters.

- Table 1 (Age Distribution) showed that patients in Group B tended to be younger, with a higher proportion of participants in the ≤20 years age group compared to Group A. However, the difference in age distribution between the groups was not statistically significant ($p = 0.100$), indicating that both groups were comparable in terms of baseline age characteristics.

- Table 2 (Gender Distribution) revealed that all patients in Group A were male, while Group B had one female participant. The difference in gender distribution was not statistically significant ($p = 0.99$), suggesting that gender distribution was relatively balanced across groups.

- Table 3 (Site Operated) indicated that the parasymphysis and angle of mandible were the most operated fracture sites in both groups. Although Group B had a few additional cases involving the condyle and sub condyle regions, the difference in anatomical site distribution was not statistically significant ($p = 0.553$).

- Table 4 (Osteocalcin Levels – Intergroup Comparison) showed that postoperative osteocalcin levels increased in both groups, but the increase was more pronounced in Group A, indicating enhanced osteoblastic activity. The mean difference in osteocalcin levels between the groups was statistically significant ($p = 0.002$), supporting the bone mineralizing effect of intranasal salmon calcitonin spray.

- Table 5 (Osteocalcin Levels – Intragroup Comparison) demonstrated a statistically significant increase in osteocalcin levels from preoperative to postoperative period within both groups ($p = 0.008$ for each). However, the magnitude of increase was substantially higher in Group A, reinforcing the clinical efficacy of calcitonin spray in stimulating bone healing.

- Table 6 (Moed Radiographic Scoring Index) evaluated fracture healing at 30 days postoperatively. While both groups had patients in Level III, Group A had more patients in Level IV (complete radiographic healing) and fewer in the lower levels compared to Group B. Although the difference was not statistically significant ($p = 0.278$), the clinical trend favored improved radiographic healing in Group A.

- Table 7 (VAS Score Comparison) assessed postoperative pain at multiple time intervals. A consistent trend of better pain control in Group A was observed, especially during the early postoperative days (Day 1 to Day 3). By Day 30, most patients in both groups were pain-free. Although no statistically significant differences in VAS scores were observed at any time point, the clinical trend suggested superior analgesic efficacy of calcitonin nasal spray in the early postoperative phase.

Discussion:

Calcitonin, also known as thyrocalcitonin, is produced in the thyroid gland's parafollicular cells. It promotes healthy bone turnover by reducing bone resorption (Marshall et al., 2008). The normal secretion and plasma levels of calcitonin are 0.5 mg/day and 0.2 ng/ml. Calcitonin hormone can be safely administered through different routes, such as oral medication (Hamdy et al.,) and nasal spray (Trovas et al.,), to promote bone healing. Calcitonin has been used to facilitate bone healing in various clinical indications, including osteoporosis (Trovas & Hak et al), vertebral fracture (Pagonis et al.,), and odontoid fracture (Darakchiev et al.,). Salmon calcitonin, a hormone known for its anti-resorptive properties, has been explored as an adjunct therapy to promote bone healing. Calcitonin is commercially produced from salmon, eel, porcine, and human sources, with salmon being the most potent (Plosker et al.,). Chesnut et al. in their randomized controlled trial involving 1,255 postmenopausal osteoporotic suggested that 200 IU OF calcitonin nasal spray was effective in reducing vertebral fracture risk.[24] El-Husseini et al., in their prospective study have highlighted benefits of calcitonin nasal spray when used as an adjunct in management of transplant related bone loss especially in patients with juvenile osteoporotic patients.[30]

A RCT conducted by Roy A. et al., included 14 patients (seven study and seven control) with mandibular fractures. Among the subjects, 13 (92.9%) were males and 1 (7.1%) female. The mean age of the subjects included in the study group was 28.1 ± 3.05 years, while that for the control group was 32.0 ± 4.02 years. The distribution of fracture diagnosis was as follows: four (57.1%) parasymphysis, two (28.6%) body, and one (14.3%) angle for the study group; whereas five (71.4%) parasymphysis, one (14.3%) body, and one (14.3%) angle for the control group.

In our study, both Group A and Group B consisted of 9 patients each, ensuring balanced sample sizes for statistical analysis. The age distribution showed a relatively younger population in Group B, included 8 males (88.9%) and 1 female (11.1%), with higher representation in the ≤20 years category (55.6% vs. 11.1). While Group A was skewed toward older male patients (100%), particularly in the 31–40 years range (55.6% vs. 22.2%). The mean age was slightly higher in Group A (39.17 ± 14.13 years) compared to Group B (33.33 ± 12.64 years). In the anatomical site distribution the parasymphysis region was the most frequently involved site in both Group A (55.6%) and Group B (44.4%), followed by the mandibular angle (44.4% in Group A and 33.3% in Group B. Fractures involving the condylar and subcondylar regions

were observed only in Group B (11.1% each), whereas fractures of the body, symphysis, and ramus were exclusive to Group A.

As per a study performed by Vs K et al. in almost all cases of osteoporosis, the bone formation remains at least partially coupled to the bone resorption, even though the resorption rate can far exceed the formation. Osteocalcin is synthesized during the bone formation and it exhibits a compact, calcium dependent, alpha helical conformation, in which the Gamma Carboxyglutamic Acid (GLA) residues bind and promote absorption of hydroxyapatite in the bone matrix. In this way, bone mineralization take place. The deficiencies of calcium and phosphorus in osteoporotic women lower the formation of the hydroxyapatite crystals, which in turn makes the free osteocalcin to circulate in the blood. This may explain the increased concentrations of osteocalcin in the sera of osteoporotic post-menopausal women. The bone mineral density in the hip region was measured by the DXA scan. In their study serum osteocalcin was estimated by ELISA (Osteocalcin ELISA Kit manufactured by Bio Source, Europe, SA). Roy et al assessed that the mean preoperative serum osteocalcin levels were 61.3 ± 7.5 ng/dl in the control group and 66.5 ± 9.1 ng/dl in the study group. The difference between these two mean values was not statistically significant. In the postoperative period, there was a significant difference in mean serum osteocalcin values between the study and control groups (67.8 ± 8.9 ng/dl vs 57.7 ± 6.29 ng/dl, respectively; $p < 0.05$). The level of serum osteocalcin increased from 66.5 ± 9.1 to 67.8 ± 8.9 ng/dl in the study group, whereas in the control group it decreased from 61.3 ± 7.5ng/dl to 57.7 ± 6.2ng/dl. Ivaska, K.K et al. analysed hip and other fractures separately, there seemed to be a decrease in serum osteocalcin after hip fractures in the early post fracture period. Their explanation for the decrease in serum osteocalcin was a possible trauma-related elevation in serum cortisol. The biosynthesis of OC is suppressed by glucocorticoids the levels decrease after administration and are generally lower in women with recent hip fracture than in elderly controls.

In our study, serum osteocalcin levels a reliable biochemical marker of osteoblastic activity and bone formation were evaluated preoperatively and postoperatively to assess the impact of intranasal salmon calcitonin on bone healing following ORIF in mandibular fractures. Preoperatively, the study group demonstrated slightly higher osteocalcin levels (11.87 ± 9.72 ng/dl) compared to the control group (8.44 ± 5.29 ng/dl), though this baseline difference was not statistically significant. Postoperatively, however, a marked elevation in osteocalcin was observed in the study group (15.72 ± 9.08 ng/dl), whereas the control group exhibited only a modest increase (9.18 ± 5.70 ng/dl). Importantly, the mean difference in osteocalcin levels was

significantly greater in the calcitonin group (3.84 ± 3.28 ng/dl) compared to controls (0.74 ± 0.58 ng/dl), with a p-value of 0.002, confirming a statistically significant enhancement in bone-forming activity attributable to calcitonin administration. These findings underscore the potential of intranasal salmon calcitonin as an effective adjunctive agent in promoting early osteogenesis and enhancing the quality of bone repair in surgically managed mandibular fractures.

Many randomized controlled trials have examined the effects of calcitonin on bone mass in premenopausal women, women at the time of menopause, and men and women with low bone mass or osteoporosis. The study performed by Reginster JY et al., consistently indicated that both injectable and intranasal forms of calcitonin can effectively prevent bone loss in women during the menopausal transition, in the immediate postmenopausal period, and later in life. Bone loss prevention has been demonstrated at various skeletal sites, including the spine, forearm, and hip, with the most substantial data available for the spine. The magnitude of calcitonin's effect appears similar in both preventive and therapeutic contexts; however, treatment-related improvements are most pronounced when initiated close to the onset of menopause. Notably, overall fracture risk was reduced by 57%, highlighting calcitonin's potential role in mitigating osteoporotic fractures.[59]

Radiographic assessment performed in a study by Roy et al at the 12th postoperative week in the control group found one patient (14.3%) at level II and six (85.7%) at level III. In their study group, five (71.4%) were assessed as level III and two (28.6%) as level IV. Better bone healing scores were found in the study group, but the difference was found to be statistically insignificant. In another randomized, double-blind, placebo-controlled clinical trial by Podichetty et al. involving 260 independently living patients aged 65 years and older with acute hip fractures, the efficacy of intranasal salmon calcitonin (200 IU daily for three months) was evaluated. While no significant difference in calcaneal bone mineral density (BMD) was observed between the calcitonin and placebo groups, a notable benefit was seen in a subset of 99 patients who underwent internal fixation with screws or nails. In this subgroup, radiographic evidence of fracture union at three months postoperatively was significantly higher in the calcitonin group (84%) compared to the placebo group (63%) (P = 0.029), indicating a 20% absolute improvement in bone healing.[28]

Radiographic evaluation of fracture healing in our study on postoperative day 30 was conducted using the Moed Scoring Index to compare outcomes between Group A (salmon

calcitonin nasal spray) and Group B (control). In Group A, a more favorable distribution of healing scores was observed, with 44.4% of patients achieving Level III healing characterized by increased callus formation and an obscure fracture gap whereas 22.2% reaching Level IV, indicating complete radiological union with abundant callus and an indistinct fracture line. In contrast, Group B had no patients attaining Level IV healing. Instead, the majority (55.5%) remained at Level II, reflecting limited callus formation and a visible fracture gap, while 44.4% reached Level III. Although the intergroup difference did not reach statistical significance ($p = 0.278$), the higher proportion of patients in Group A achieving advanced healing stages suggests a clinically meaningful trend toward enhanced radiological bone healing with adjunctive use of intranasal salmon calcitonin following ORIF for mandibular fractures.

Both central and peripheral mechanisms of calcitonin's analgesic effect have been identified; the former primarily involves serotoninergic and catecholaminergic receptor systems, while the latter involves the stimulation of increased release of beta-endorphin, a neuropeptide that acts as an agonist on the body's opioid receptors. Because calcitonin's potency has been demonstrated to be superior to that of morphine also has fewer side effects. Its analgesic impact has been used to relieve pain, even in cancer patients who are terminally ill. A clinical, double-blind controlled study conducted by Kaskani E. et al. evaluated the efficacy of nasal salmon calcitonin in relieving post vertebral fracture pain. 32 men and 68 postmenopausal women with a mean age of 76 and 71 years, respectively, who had sustained a nontraumatic vertebral fracture were included in the trial. Clinically, each patient exhibited severe pain localized at the site of the collapsed vertebra. The correlation between the radiographic findings and the reported pain was deemed indicative of a recent fracture. The patients were hospitalized for a period of 28 days. Pain was reduced dramatically in the group receiving calcitonin ($p \sim 0.001$). The analgesic effect of nasal calcitonin was negatively associated to the number of paracetamol tablets requested by the patients ($p \sim 0.001$). Pain rating on the VAS, showed that the most patients were gradually able to gain full mobility after the first week of calcitonin treatment even when pain was rated below 7 on the VAS scale.[31] Additionally, a study conducted by Huusko TM et al (2002) concluded that although the difference in postoperative pain intensity, measured by the visual analog scale (VAS), did not reach statistical significance (median VAS: 0 mm in the calcitonin group vs. 4 mm in the placebo group; $P = 0.15$), the trend still favoured better pain control in the calcitonin group.[25] In a double-blind, randomized, placebo controlled study by Podichetty et al the effectiveness of calcitonin nasal spray on symptoms

and function in patients with lumbar canal stenosis were assessed. Fifty-five patients with clinical lumbar canal stenosis (pseudo claudication), and pain intensity index (VAS) of 6 were randomized to either placebo or intranasal calcitonin daily for 6 weeks, followed by an open label 6-week extension, during which all patients received active drug. 50% reduction in pain from baseline to 6 weeks,12 of 29 (41.37%) of calcitonin patients were considered responders in comparison to 7 of 18(38.88%) placebo patients (P =0.4238).[28]

In our study postoperative pain intensity, assessed using the Visual Analog Scale (VAS) on days 1, 3, 7, and 30, revealed a consistent clinical trend of improved pain control in Group A (salmon calcitonin nasal spray) compared to Group B (control). On day 1, more patients in Group A reported lower pain scores, with nearly half experiencing only mild pain, unlike Group B, which showed moderate to severe pain distribution. By day 3, while Group B had more pain- free patients, Group A demonstrated a steady reduction in pain, maintaining a more uniform response. Pain relief significantly improved in both groups by day 7, and by day 30, nearly all patients were pain-free. Group A exhibited early and more consistent pain relief, suggesting a beneficial clinical impact of calcitonin on postoperative pain management.

Research on salmon calcitonin, stating its role in physiological outcomes and its numerous clinical uses, is gaining more and more attention. Calcitonin either in spray or an injectable form has been used in various other pathologies such as osteoporosis, CGCG, Paget's' disease and other orthopedic fractures. However, there is a paucity of research on use of salmon calcitonin nasal spray in maxillofacial fractures. Therefore, to contribute additional clinical data and widespread administration of these spray as a bone mineralizing and analgesic agent in the field of maxillofacial surgery, a study with larger sample size and longer follow up periods are recommended.

Conclusion

This study underscores the therapeutic efficacy of salmon calcitonin nasal spray as a practical and effective intervention for enhancing bone healing and managing postoperative pain in patients with osteoporosis and related bone disorders. Calcitonin nasal spray, as evidenced by previous studies such as those by Chesnut CH et al.,[24] demonstrated a 33% reduction in vertebral fracture risk and a 1–1.5% BMD over a 60-month period. The findings align with these outcomes, showing a clinically observable trend toward & improved bone healing and pain reduction in patients receiving calcitonin nasal spray.

Group A was administered calcitonin nasal spray, showed positive radiological and clinical healing results. With 22.2% of patients classified at Level IV, which denotes full fracture union with extensive callus production, a larger percentage of patients in Group A reached advanced healing stages. None of the patients in Group B, however, were able to reach Level IV healing condition. These results were further supported by the biochemical analysis, which revealed that patients who received calcitonin spray had significantly higher levels of osteocalcin, rising from 11.87 ± 9.72 ng/ml before surgery to 15.72 ± 9.08 ng/ml after, indicating a marked increase in osteoblastic activity and bone turnover. Thereby concluding an effective role of calcitonin nasal spray as a bone mineralizing agent.

The therapeutic efficacy of calcitonin has been further enhanced by developments in delivery technologies. To enhance drug absorption and extend nasal retention, chitosan-based nasal formulations and nanoparticle-based preparations have been created. These developments improve patient adherence, especially in the long-term care of osteoporosis and reduce common consequences such nasal septum perforation. Furthermore, the use of smart nasal devices with sensors to track medication administration and dose presents encouraging possibilities for individualized treatment plans. Calcitonin’s safety profile remains favourable, with Wells' meta-analysis confirming minimal carcinogenic risk with prolonged use.[15]

Adding salmon calcitonin nasal spray to maxillofacial fracture has major clinical advantages for pain relief, bone mineralization and fracture prevention. When combined with cutting-edge administration methods, its dual action on bone growth and resorption maximizes treatment efficacy while reducing systemic side effects. To validate these results and ascertain the best dosage schedules and long-term safety profile of calcitonin nasal spray in a range of patient demographics, more extensive multicenter studies with prolonged follow-up are required.

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ANNEXURE 1

ETHICAL COMMITTEE CLEARANCE FORM

SANTOSH
Deemed to be University
(Established u/s 3 of the UGC Act, 1956)

F. No. SU/2023/2480[21] Dated: 26.09.2023

Subject: Grant of Ethical Clearance for Thesis Protocol Topic "Evaluation of efficacy of intranasal salmon calcitonin nasal spray as a bone mineralizing agent after open reduction and internal fixation in patients with mandibular fractures:A prospective clinical study", submitted by **Dr. RANI RAGINEE RAJHANS,** MDS student of Batch 2022-2023, Department of **ORAL & MAXILLOFACIAL SURGERY**.

*****

With reference to his/her request for grant of Ethical Clearance for the Thesis Protocol entitled "Evaluation of efficacy of intranasal salmon calcitonin nasal spray as a bone mineralizing agent after open reduction and internal fixation in patients with mandibular fractures:A prospective clinical study", **Dr. RANI RAGINEE RAJHANS** is informed that the Thesis Protocol submitted by him/her was considered by the **Screening Committee** of the Santosh Dental College & Hospital in its meetings held on 07.02.2023 & 08.02.2023. The recommendations of the **Screening Committee** were considered in detail by the Institutional **Ethics Committee** in its meeting held on **23.09.2023** and the same was **approved** by the **Ethics Committee**.

He /She is informed accordingly for further necessary action.

[DR. NARESH SHARMA]
REGISTRAR

Dr. RANI RAGINEE RAJHANS
MDS student of batch 2022-2023
Department of ORAL & MAXILLOFACIAL SURGERY
Email: rajhansraginee@gmail.com

Copy to:

1. The Vice Chancellor
2. The Dean, SDC&H
3. The Dean – Research
4. The Dean – Academics
5. The Director - IQAC
6. **Dr. Mayank Singhal** (Guide)
7. HOD of **ORAL & MAXILLOFACIAL SURGERY**

ANNEXURE 2

ANTI-PLAGIARISM REPORT

DR. Rani Raginee Rajhans

"THE EVALUATION OF THE EFFICACY OF INTRANASAL SALMON CALCITONIN NASAL SPRAY AS A BONE MINERALIZ...

Santosh University, Ghaziabad

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ANNEXURE 3

CASE RECORD PROFORMA

NAME:

AGE:

SEX

OPD NUMBER

OCCUPATION:

ADDRESS:

CHIEF COMPLAINT:

HISTORY OF PRESENTING ILLNESS:

MEDICAL HISTORY:

DRUG HISTORY:

PAST DENTAL HISTORY:

PERSONAL HISTORY:

GENERAL PHYSICAL EXAMINATION

BP: Pulse: Temperature:

Respiratory rate:

Axial Skeleton: Appendicular Skeleton:

Glasgow Coma Scale

Associated Injuries:

LOCAL EXAMINATION

EXTRAORAL

Inspection:

Upper Third of the face:

Middle Third of the face:

Lower third of the face:

TMJ:

Maximal Interincisal opening:

Palpation:

Upper Third of the face:

Middle Third of the face:

Lower Third of the face:

TMJ:

INTRAORAL

Inspection

Dentition

Occlusion

Palpation

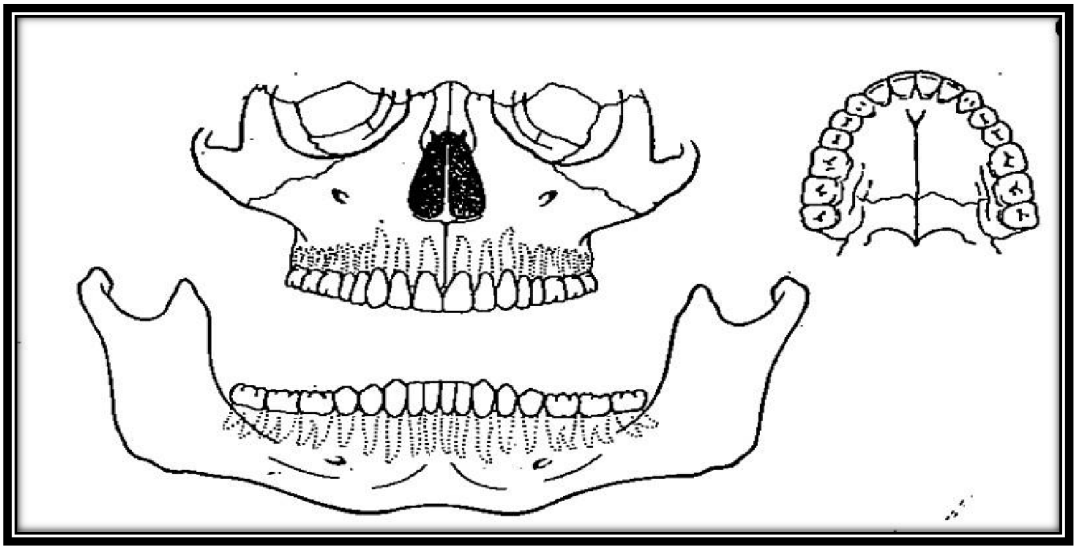
Intraoral soft tissue injury:

PROVISIONAL DIAGNOSIS:

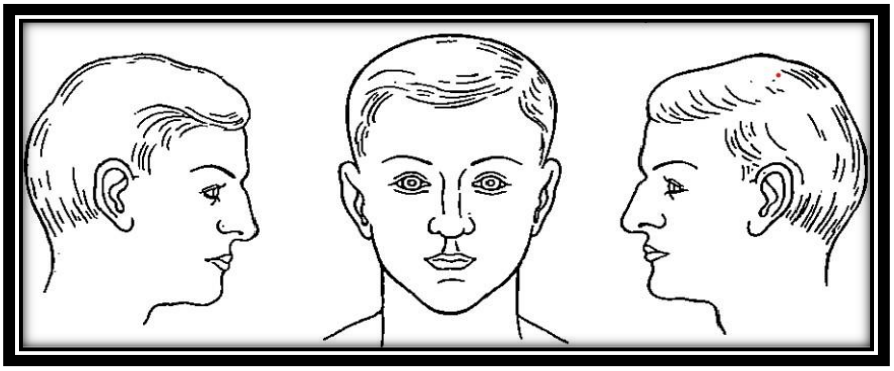
RADIOGRAPHIC EVALUATION:

FINAL DIAGNOSIS:

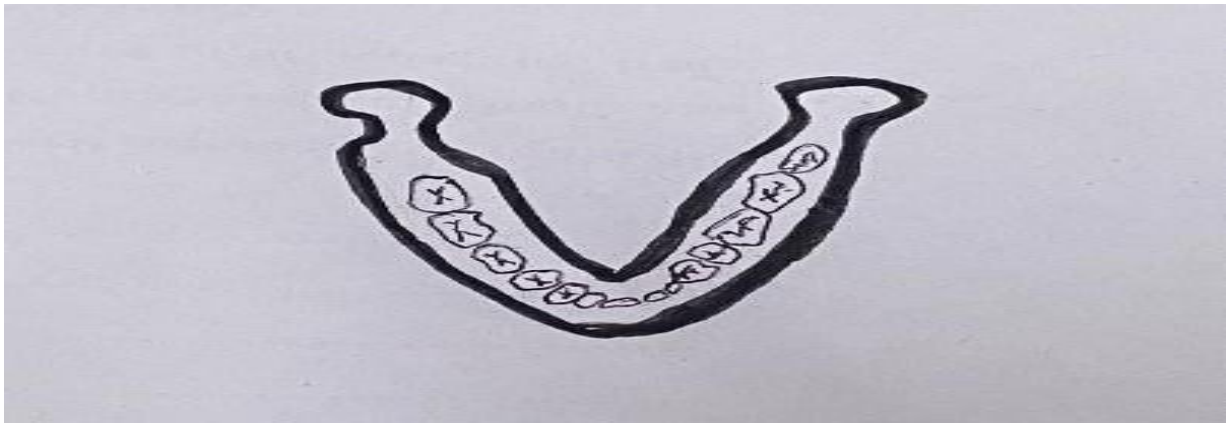
ADVISED TREATMENT PLAN:



Pictorial representation of facial injuries:



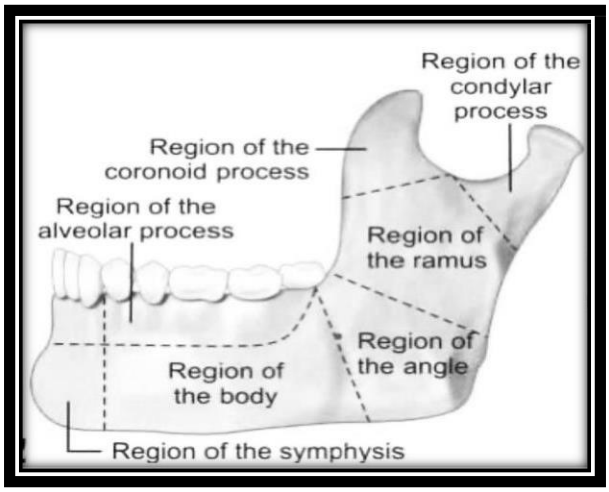
Mandibular Fractures Classification



MANDIBULAR FRACTURE CLASSIFICATION

1. Simple
2. Compound
3. Comminuted
4. Complicated
5. Impacted
6. Greenstick
7. Pathological

A. Anatomical location


Region of the condylar process
Region of the coronoid process
Region of the alveolar process
Region of the ramus
Region of the angle
Region of the body
Region of the symphysis

B. Based on teeth in relation to the fracture line

Class I – Teeth are present on both sides of the fracture line Class II – Teeth are present only on side of the fracture line Class III – Patient is edentulous

C. Based on direction of fracture line

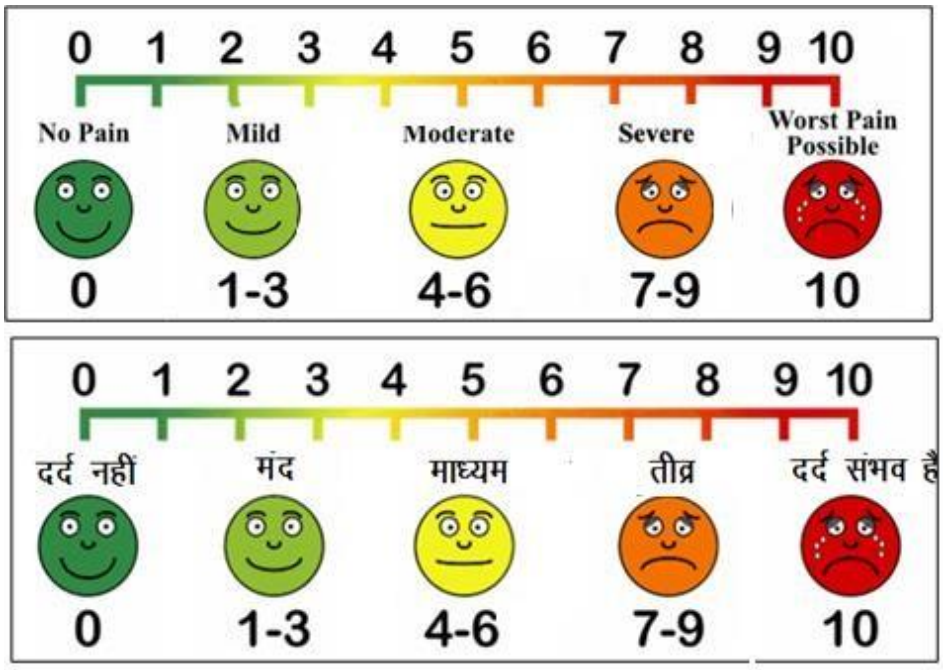
1.Favorable fracture

2.Unfavorable fracture

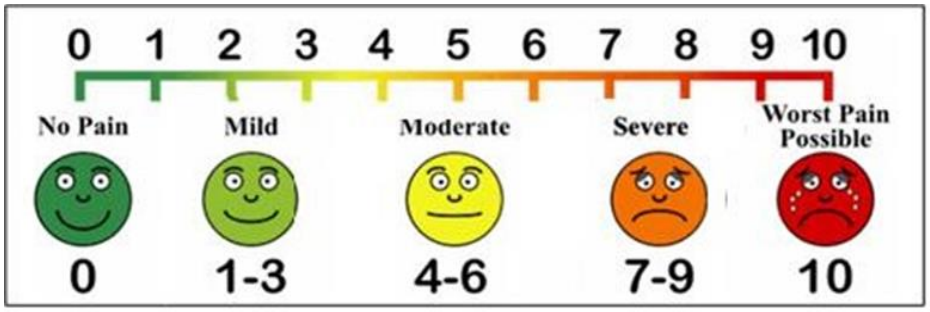
Table 1: Serum osteocalcin levels in the study vs control groups

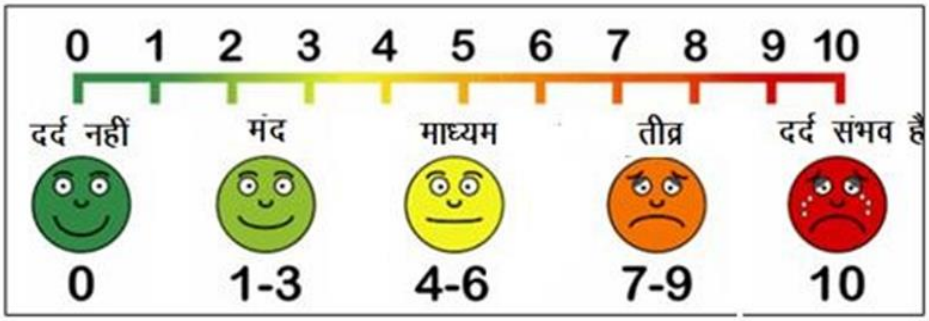
Variables	ng/ml
Osteocalcin Preoperative	
Osteocalcin Postoperative	

VAS Scale

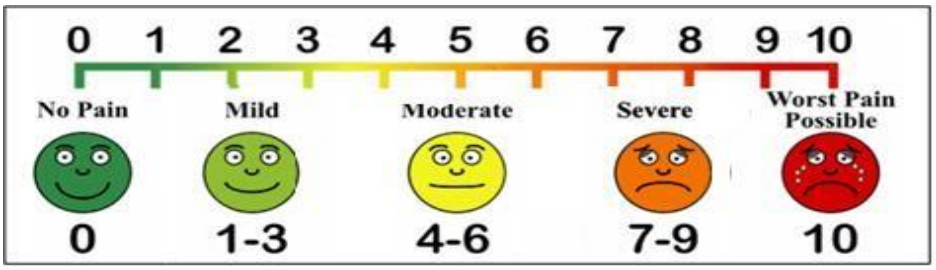


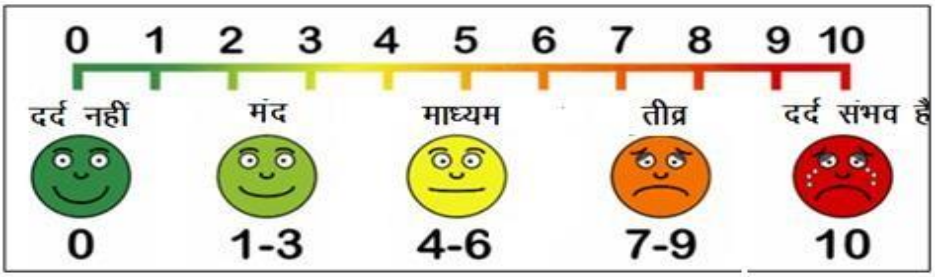
POSTOPERATIVE DAY 1
0=NO PAIN
1-3 =MILD PAIN
4-6 =MODERATE PAIN
7-9 =SEVERE PAIN
10 =WORST PAIN POSSIBLE



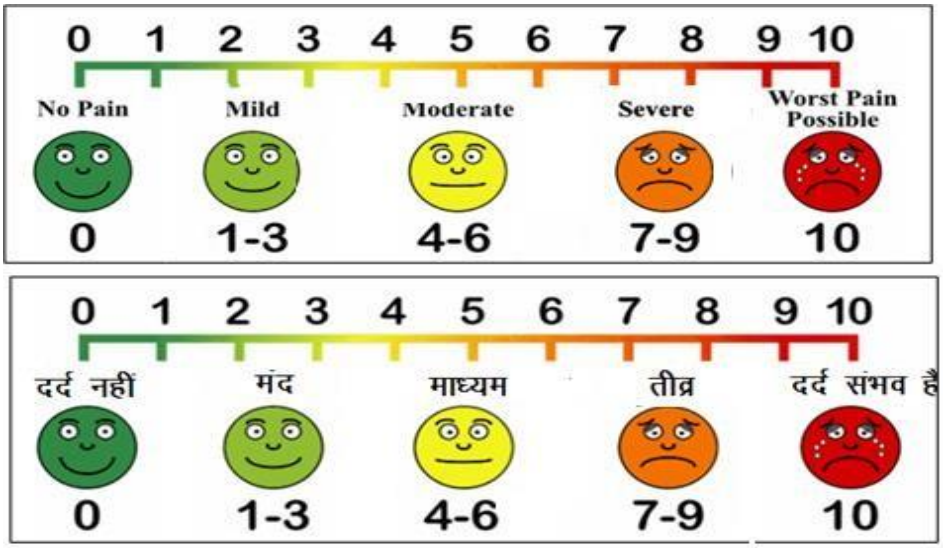


POSTOPERATIVE DAY 3
0=NO PAIN
1-3 =MILD PAIN
4-6 =MODERATE PAIN
7-9 =SEVERE PAIN
10 =WORST PAIN POSSIBLE





POSTOPERATIVE DAY 7
0=NO PAIN
1-3 =MILD PAIN
4-6 =MODERATE PAIN
7-9 =SEVERE PAIN
10 =WORST PAIN POSSIBLE



POSTOPERATIVE DAY 30

0=NO PAIN

1-3 =MILD PAIN

4-6 =MODERATE PAIN

7-9 =SEVERE PAIN

10 =WORST PAIN POSSIBLE

Table 2: Pain scores

Pain	**Day 1st**	**Day 3rd**	**Day 7th**	**Day 30th**

Table 3: Radiographic evaluation (Moed index):

		4th WEEK	**8th WEEK**	**12th WEEK**
Levels	1: No callus, clear fracture gap, slightly fuzzy boundaries of fracture ends(1point)			
	2: Few calluses, clear fracture gap(2point)			
	3: More calluses, obscure still existent fracture gap(3points)			
	4: Indistinct fracture gap, large number of calluses, completely connected fracture ends			

Table 5: Complications (if any):

	1st week postoperative	4th week postoperative
Complications		

1=Rhinitis

2=Nasal irritation

3=Epistaxis

ANNEXURE 4

INFORMED CONSENT

DEPARTMENT OF ORAL AND MAXILLOFACIAL SURGERY

SANTOSH DENTAL COLLEGE HOSPITAL, GHAZIABAD

"THE EVALUATION OF THE EFFICACY OF INTRANSAL SALMON CALCITONIN SPRAY AS A BONE MINERALISING AGENT AFTER OPEN REDUCTION AND INTERNAL FIXATION IN PATIENTS WITH MANDIBULAR FRACTURES: A PROSPECTIVE CLINICAL STUDY"

I, Mr./Ms

……..

S/O,D/O,W/O.

……..

A resident of

…… ..

have been informed about all the benefits and risks during and after the surgical procedure. I am willingly participating in the study conducted by the Department of Oral and Maxillofacial Surgery, Santosh Dental College, and Hospital.I should choose to withdraw from this study at any point; I will be free to do so after giving prior information to the concerned surgeon.

Signature of Surgeon In-charge Signature of Patient

Date: Date:

Signature of Parent/Guardian

Date:

शोध विषयस्वीकवि पत्र

मुँह/जबड़ा शल्य चिकित्साविभाग

संतोष दन्त महाविद्यालय एवं अस्पताल,ग़ाज़ियाबाद

“मेन्डिबुलर फ्रैक्चर वाले रोगियों में ओपन रिडक्शन और इंटरनल फिक्सेशन के बाद बोन मिनरलाइजिंग एजेंट के रूप में इंट्रानैसल सैल्मन कैल्सीटोनिन नेजल स्प्रे की प्रभावकारिता का मूल्यांकन: एक संभावित क्लिनिकल अध्ययन। ”

मै,श्/श्म्/.....

.....

पुत्र/पुत्री

.....

.....

निवासी.....

.....

.....

.....

...

इस शल्य चिकित्सा के दौरान और उसके बाद होने वाले लाभ और जोखिम से भली भाति अवगत कराया गया है ।मैं अपनी स्वेछा से मुँह जबड़ा शल्यचिकित्सा विभाग, संतोष दन्त महाविद्यालय एवं अस्पताल में आयोजित इस अध्ययन में अपना योगदान करना चाहता/चाहती हु। यदि में अध्ययन से किसी भी समय अलग होना चाहू तो चिकित्सा को सूचित करने के पश्चात अलग हो सकता/सकती हूँ।

चकित्सा के हस्ताक्चर **मरीज के हस्ताक्चर**

MASTER CHART

Preoperative Group A (Salmon Calcitonin Nasal Spray)					Postoperative Group A (Salmon Calcitonin Nasal Spray)																										
S.NO	AGE	SEX		OL	OL	Radiograph				VAS																					
						D30				D1						D3					D7					D30				
	YRS	M/F	OS on Mandible	ng/ml	ng/ml	L1	L2	L3	L4	V1	V2	V3	V4	V5	V1	V2	V3	V4	V5	V1	V2	V3	V4	V5	V1	V2	V3	V4	V5
1	19	M	Symphysis	5.81	6.41	0	0	3	0	0	0	0	0	1	0	1	0	0		0	0	0	0	0	0	0	0	0	0	
2	24	M	Body and Angle	14.2	16	0	0	0	4	0	1	0	0	0	0	1	0	0		0	0	0	0	0	0	0	0	0	0	
3	27	M	Left Parasymphysis,Right Angle	3.53	14.7	0	0	0	4	0	0	1	0	0	0	0	1	0		0	0	0	0	0	0	0	0	0	0	
4	27	M	Left Ramus	17.7	24	0	0	3	0	0	0	0	1	0	0	1	0	0		0	0	0	0	0	0	0	0	0	0	
5	32	M	Right Parasymphysis	11.9	14.4	0	0	3	0	0	0	0	0	1	0	1	0	0		0	0	0	0	0	0	0	0	0	0	
6	32	M	Left Parasymphysis	13.7	17.2	0	0	3	0	0	1	0	0	0	0	0	1	0		0	1	0	0	0	0	0	0	0	0	
7	36	M	Left Parasymphysis,Right Angle	2.03	7	0	2	0	0	0	0	0	1	0	0	1	0	0		1	0	0	0	0	1	0	0	0	0	
8	36	M	Left Angle	4.7	7.24	0	2	0	0	0	0	0	1	0	0	0	1	0		1	0	0	0	0	0	0	0	0	0	
9	37	M	Right Parasymphysis	33.3	34.5	1	0	0	0	0	0	0	1	0	0	1	0	0		1	0	0	0	0	0	0	0	0	0	

Preoperative Group B (without Salmon Calcitonin Nasal Spray)					Postoperative Group B (without Salmon Calcitonin Nasal Spray)																										
S.N0	AGE	SEX	OS On Mandible	OL	OL	Radiograph				VAS																					
						D30				D1						D3					D7					D30				
	YRS	M/F		ng/ml	ng/ml	L1	L2	L3	L4	V1	V2	V3	V4	V5	V1	V2	V3	V4	V5	V1	V2	V3	V4	V5	V1	V2	V3	V4	V5	
1	17	M	Right Parasymphysis	5	5.25	0	2	0	0	0		1				1				1					1					
2	17	M	Left Condyle	6	6.12	0	0	3	0			0	1				1				1				1					
3	17	M	Left Subcondylar,Right Parasymphy	12.56	14.44	0	0	3	0			1					1			1					0					
4	17	M	Right Angle	14	15.12	0	0	3	0	0	0	0	1		0	0	0	0												
5	18	M	Left Angle	7	7.13	0	2	0	0	0	0	0	1		0	0	0	0			0									
6	25	F	Left Parasymphysis	6	6.8	0	2	0	0			1				1				1					0					
7	30	M	Right Parasymphysis	3.53	4	0	2	0	0			1				1														
8	36	M	Left Body of Mandible	3.43	4.12	2	2	3	3	0	0	0	0	1	0	0	0	0												
9	38	M	Right Condyle,Left Angle Fracture	18.5	19.7	1	2	4	4	0	0	0	0	1	0	0	0	0												

OS- OPERATED SITE

OL- OSTEOCALCIN LEVELS (nanograms per milliliter)

VAS - Visual analogue scale

Radiograph D/30= Day 30

The Moed scoring index
- L1=Level I: (1 point) i.e., 1mm hyperechoic manifesting as no callus, clear fracture gap, slightly fuzzy boundaries at the fracture ends.
- L2= Level II: (2 point) i.e. 0.5-0.7mm hypoechoic manifested as few calluses and obscure but still existent fracture gap;
- L3=Level III: (3 point) i.e. more calluses and obscure still existent fracture gap;
- L4=Level IV: indistinct fracture gap, large number of callus and completely connected fracture ends.

D1= DAY 1
D3= DAY 3
D7= DAY 7
D30= DAY 30
V1= No Pain
V2= Mild Pain
V3= Moderate Pain
V4= Severe Pain
V5= Worst Pain Possible